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OPERATOR: Thank you for standing by, and welcome to the GSK Q3 results meeting analyst and investors conference call. At this time, all participants are in a listen-only mode. There will be a presentation today followed by a question-and-answer session. (OPERATOR INSTRUCTIONS).

In order that we may accommodate as many callers as possible today, can I please ask you to limit your questions to two or three. I would like to advise you the call is being recorded Thursday, 26 of October, 2006.

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I would now like to hand the conference over to your speaker for today, Mr. JP Garnier. Please go ahead, sir.

JP GARNIER, CEO, GLAXOSMITHKLINE: Thank you and welcome to all. I am here with David Stout, President of Pharmaceuticals, and Julian Heslop, our Chief Financial Officer. They will address to you some of the aspects of our business and our financial performance.

I'm going to make some very, very brief remarks, first on the strong financial results. You have seen the sales and the EPS up 21% in comparative terms -- I think that's ahead of expectations -- and also the very positive financial outlook for the Company, in terms of the guidance that has been raised to reflect the current trend of our business, but also the doubling of the share buyback and the increase in the dividend. We feel that at this point, having put aside some of the risks to our cash position such as the tax settlement and the like, we're in a position to give back to the shareholders without having to incur additional debt. So, this is kind of the plan for the future.

In terms of the key product news, I'm trying to pick and choose in there what's really important, because the some of the news are more important and will have more impact on the future of the Company than others. The ones I selected for you -- and that's my personal opinion -- is first of all, Tykerb and Cervarix basically on track.

I know Cervarix we aimed at December, we estimated. But this was not a trial driven by the clock, where you normally can forecast pretty accurately; this was an event-driven trial. Therefore, we do our best to guess when we are going to spot those cases of infection. They come at a different pace every month, and we guessed okay but we didn't guess completely right. That's why we had to slip into next year to finish the file.

But the good news is we now have enough cases; the clinical trial is officially ending soon. We start to put the file together. There is considerable amount of data on -- we certainly are going to study it so

that we position it for a unique profile on the issues we have discussed with you before, whether it's cross-protection or age bracket of people benefiting from -- of females benefiting from the vaccine. So, this is a very important phase, and we are very encouraged by what has been happening so far.

Of course, Tykerb filing in the US and, more importantly, I think the relative enthusiasm of the FDA for the file is giving me great confidence in the future of this compound.

Coreg CR is not going to win us the Nobel prize, but it's a tremendous commercial opportunity. It's not just a line extension, which is always nice, and we have done well with those in the past; it's a product that opens up the antihypertensive market, which is probably 5 or 10 times bigger than the current entry market for Coreg, which is congestive heart failure. So we couldn't really compete in the antihypertensive market because of the BID schedule of Coreg, which makes it far less convenient than all the once-a-day drugs. Once-a-day is a must in the antihypertensive market. That's what we have now. So we are very excited, and we will launch in a big way this drug in the early part of the next year.

Then, FluLaval is an approval that is important for us. Not only it increases immediately the amount of flu vaccine we can sell in the US but, more importantly, it unlocks a key element of our capacity for pandemic. As you know, we are hot and heavy negotiating deals on pandemic. You heard about Switzerland. We signed another one with an Asian nation that doesn't wish to be identified. We are in the last steps. Between now and Christmas, I expect that we will probably sign a few more in Europe and elsewhere.

Now, one more thing. Promacta -- I know there is a lot of news on Promacta. The bottom line is ITP -- the Phase III trial is very interesting, because not only we confirmed Phase II in spades, we met the primary endpoint of increasing the number of patients with a 50,000 platelet count. But, more importantly, we also showed a clinical effect in terms of comparing with placebo. We showed that the bleeding rate is far less.

We can't tell you much more. Don't ask questions about the data, because I can't answer them. We are going to have to go to Medical Congress and unveil the news.

But we have kind of given you, certainly, the headlines. The headlines are good. Those indications are important -- good data on liver as well. Chemo -- we have got to go back. But, contrary to what analysts have said, chemo is an intermittent treatment. It's not necessarily the biggest one, in terms of market tensional potential of Promacta.

As far as the filing is concerned, we have said all along we are in discussion with the FDA. The fact that we have shown now in a Phase III trial that we are, in effect, on the clinical endpoint is meaningful. Whether that's going to be enough, I don't know.

Pazopanib -- good surprise. The renal cell carcinoma drug performed extremely well. This was an advanced renal cell cancer trial, and the independent review board told us that, because of the very high

efficacy of the drug, we had to put the placebo patient on the drug. So they interrupted -- they didn't interrupt the trial, really, but they changed the design and said, look, you've got to cancel the placebo arm; it's unethical. This patients are not benefiting from pazopanib, which is showing a very, very interesting profile, very interesting. Probably the next Tykerb for us.

Then, the new generation flu -- that is commercially very meaningful, and I'll tell you why. This is a huge market where there is one problem with the classic flu, and that is that the elderly folks, people in their 70's and 80's -- their immune system goes down a bit, and many of them are not fully protected by classic flu vaccine.

This new generation flu, Flu Plus, is showing better coverage, higher T-cell response, better antibody reaction. Again, we will issue all this in upcoming Medical Congress, but we are very confident that we got it. We are going to do all the Phase III next year, so this is a major opportunity for us, and we will use this extensively.

So you see, on balance, even though there were a couple of disappointments on the pipeline in terms of value, I think that there is not even close. Sepsis was a longshot. It's a unfortunate it didn't make it. The DPPIV is a mixed blessing; we are so much in the back of the pack, we'll have to see what happens next. I'm not too optimistic, but in any case, I think those news were relatively modest compared to the positives.

Can I just now ask Julian to take you through the financials, and I'll be back for the questions.

JULIAN HESLOP, CFO, GLAXOSMITHKLINE: JP, thank you. Turnover in the quarter was up 7%, with pharmaceuticals up 7% and consumer up 4%. Cost of goods as a percentage of turnover was 21.7%, which was broadly in line with last year. This reflected a number of factors, including favorable price and regional mix changes and the adverse impact of higher charges related to restructuring programs.

SG&A costs excluding legal charges decreased 1%. We continue to benefit from previous restructuring programs and the tight focus on cost control. You can see in the slide I've split legal charges from the rest of SG&A. R&D expenditure increased 11% in the quarter, driven by higher restructuring charges, partly offset by lower asset impairment write-offs. Excluding these two items, expenditure increased 7%, in line with turnover growth.

Other operating income was GBP91 million, around half of last year's level, due to a reduction in asset sale profits and lower gains on the Theravance and Quest financial instruments. Overall, operating profit growth was 19%.

You can see from the next slide the profit before tax growth of 21% benefited from lower interest charges. At actual rates, it was 15%, reflecting a significant weakening in the dollar compared to the previous year. Earnings per share growth of 21% was in line with PBT growth, as a lower minority interest charge compensated for the higher tax rate this quarter.

The next slide sets out, as usual, the impact of legal and restructuring costs, asset sale profits and financial instrument movements on the results. You can see that lower legal charges this quarter were broadly offset by higher restructuring costs and lower asset sale profits. Overall, these items had no impact on the profit growth for the quarter, nor did they impact the increase in the profit margin.

Restructuring costs increased in quarter three, as the Company commenced implementation of a series of restructuring projects, particularly in manufacturing and research and development. I expect a similar level of restructuring charges in the fourth quarter.

The next chart shows that the US dollar was a key driver of the adverse currency impact on the reported results this quarter. It's also worth noting that Sterling's strength also led to adverse currency impacts in most parts of the world. If rates continue at current levels, I would expect an 8% to 9% adverse currency impact on EPS growth in the fourth quarter. Overall, my expectation for the full year is that currency will have an adverse impact on EPS growth of around 1% to 2%.

Free cash flow for the quarter was adversely impacted by a gross payment of $3.3 billion to the US Internal Revenue Service under the agreement which settled the transfer pricing dispute. We expect to discharge the remaining liabilities this year. Overall, the net cost to GSK will be $3.1 billion, which covers not only the gross federal and state payments but also the benefit of tax relief on the payments made. Net debt at the end of the quarter increased to GBP2.1 billion, primarily as a result of these tax settlement payments.

I would like to conclude with comments on dividends and share repurchases. We have reviewed the dividend policy that has been in place since the merger and have concluded, based on our earnings growth to date, that a more progressive policy is now appropriate. We have therefore announced today that we expect to pay a 2006 dividend of 48p and a 4p increase on last year. At the same time, we expect dividend cover to improve as well.

In respect to share repurchases, given our continued strong cash flow performance, we have also announced a new GBP6 billion share buyback program, and we expect it to be completed over a three-year period, including GBP2 billion over the next 12 months.

I will now hand over to David.

DAVID STOUT, PRESIDENT, PHARMACEUTICAL OPERATIONS, GLAXOSMITHKLINE: Thank you very much, Julian. For those of you following along with the slides from our website, if you would turn to the slide that is headed Q3 2006 sales by region.

As you can see, total sales in the quarter were up 7% to just under GBP5 billion. Now, leading to growth was the US business, where we had another strong quarter with 14% growth, which was led by our key growth drivers and what we have been calling our rising stars. I'll cover these products in some detail in just a few minutes. But just to remind you, this growth has included the ongoing generic erosion of Flonase, which began in the first quarter of this year, and of course, as you

know, Zofran, which loses it market exclusivity in the US in this, the fourth quarter. I'm sure you have already included that, however, into your models.

Europe continues to be a very tough environment for us, as market growth itself has slowed to under 5% this year. For ourselves, we were level to our performance of a year ago.

Patent expirations last year and this year for Lamictal, Imigran and Zofran have held back growth in Europe this year. While the patent expirations will continue to have an impact on our European business, our new product launches such as Tykerb and Cervarix and our vaccine business should give us more moment moderate growth in the near term.

In our international markets, we had some delays in the shipments of vaccines, along with some destocking in Japan, which held growth back to 3%, which is below the year-to-date growth of 7%. We think that 7% is more reflective of the run rate in the region. We had some slow growth in Canada and Australia, which are being offset by good growth in Latina and several of our Asian markets such as Korea, Taiwan and China.

Our vaccine business continues to be the major growth driver in the region. Of course, let's not forget that Japan continues to be our single biggest market opportunity, as there are very few generic risks there, and many significant new product launches coming.

Now, if we can, let's take a look at some of our key growth drivers on the next slide. You can see again together this group totaled GBP2.3 billion pounds and grew 15% during the quarter. I'm going to cover Advair, Avandia and Coreg in more detail in the next couple of slides, but you can also seen here that Valtrex and Lamictal had outstanding quarters as well. Let me also remind you that we should be filing Lamictal XR for epilepsy in the current quarter.

Our vaccine sales are distorted by some delays in our shipments which I had mentioned around international and some of our other markets, and these will now spill over into the fourth quarter. Also, our FluLaval vaccine, which was approved in early October, will be shipped during the fourth quarter, as our vaccine sales should get back to more normal growth.

On the next slide is a regional view of Seretide and Advair, and as you can see, overall, our sales exceeded GBP800 million and was growing 14%. Europe continues to be the Steady Eddie here, with good growth delivering 12% increase.

Our international markets grew 7%, primarily being affected by the big markets in Canada and Mexico. The biggest opportunity in international, however, remains in Japan, which is the second-largest market in the world, and we still have not launched Advair. We now expect to launch however, in Japan in 2007, and this should be a big boost to our international Advair/Seretide sales and to our overall global growth.

In the US, which is our biggest market, of course, growth of 17% reflects an improvement in price an mix, as well as some variation in wholesaler stocking and a portion of that reversal of the TRICARE

provision that was referred to in our earnings release. If you look at the underlying growth excluding the wholesaler stocking and the TRICARE reversal, the growth is closer to 9% to 10%.

Now, let me just take a few slides, if you would, to take you through the prescription trends and why we're confident that Advair is going to continue to be a major driver of growth. As we have said many times before, Advair growth is very seasonally affected, with the growth occurring from the early fall to the late spring and then following back during the summer periods.

As you see here on this slide, during the 2003-2004 season, our growth began in September, as always, and it peaked at the end of March. About half of that growth was then lost during the summer months until the 2004 and 2005 season began. Then, again, we saw the steady growth beginning in September. This time, it peaked in late May before falling back again, and again we lost about half of that growth.

If you look now, picking up on the 2005-2006 season, you can see everything started out normally, with the growth beginning just great in September. But unlike the previous years, our growth was interrupted less than halfway into the season, when we received a letter from the FDA requesting changes to our labeling. That's something we have discussed with you at some length in our previous calls.

Compounding the slowing was a mild winter that led to a decrease in office visits for asthma and COPD. I'm not going to try to forecast the winter weather patterns, but I think a more normal winter should increase office visits for these two conditions.

So for the 2005 and 2006 season, when we fell back, we ended up pretty much where we began the season. So as we go into the 2006-2007 season, we're starting out pretty much where we started last year. So, when you look at year-on-year comparisons, we are going to look flat until we get beyond the November timeframe. What's important is that we started off the season, as in the past, with good trends through September. We expect this to continue, and hope that we will not have the disruptions that led to last year's issues.

Now, let me share with you some of the reasons for our confidence, and why we expect Advair to continue to grow through the season. Here are some of the key initiatives that will continue to contribute to the growth in both the near and the mid-term.

Of course, the MDI launch, the metered-dose inhaler launch in the US, is already underway. We began our trade stocking in early October. We know that, while the majority of patients either prefer or they have gotten used to the Diskus device, there are some patients and physicians that prefer a metered-dose inhaler, and now they have that option; they have the flexibility with either dosage form.

We have also expanded our selling efforts, and to really capitalize on the COPD indication, we now have sales force that are completely focused and dedicated just on that indication. This is new information, so while COPD uses have been growing very well, I think we can accelerate the growth even more taking this new direction.

Looking forward, we have filed the TORCH data in US and Europe, and we hope that this is going to strengthen our label. This would, of course, be very important to our sales forces if and when it gets approved. I think we were also very pleased to the comments from the American College of Chest Physicians at their press conference last Monday on the TORCH results. As I mentioned earlier, we're expecting to launch in Japan in 2007.

We can now move on to Avandia. The Avandia family, which also includes Avandamet and Avandaryl, grew 11% overall. As you can see, Europe and international really are now making significant contributions to the family's growth, and they account for over 25% of the business and are growing 26% in quarter. This growth occurred, by the way, despite some of the supply issues that we had in international markets of Avandamet.

While we have reported sales growth of 6% in the US, the underlying growth here was really closer to 12%, as wholesalers were destocking some of the inventories that they had put in when we restocked the trade in the second quarter. While 12% growth in the US is okay, we're not satisfied with it and we expect this to improve.

So if you move to the next slide, let me cover why we're convinced that Avandia's growth will accelerate. I think first and most important is we really need to regain physician confidence in our ability to continue to supply the market. This is both at a trade level and with samples.

Two discontinuations of trade shipments of Avandamet is not acceptable to physicians, and quite frankly, I can't blame them for their response. That's why we painfully, painfully waited until July to relaunch Avandamet, so we would have the adequate levels when we returned to the market.

We are back now, and day by day, we're winning physicians back. But it's going to take some time to win them all. We can win them back, though, given the strength of the product and the new indications and the new data that is emerging.

Avandia is being used earlier in the treatment of diabetes, and with Avandamet's first-line indication and the approval of Avandaryl on Tuesday of this week for first-line treatment, we expect that the trend is going to continue. This is being supported also, by the way, by treatment guidelines that call for earlier use of TZDs in combination medicines.

Of course, nothing is more compelling than outcomes data, and we are now starting to get the output from our investment of six years ago in the big landmark outcomes trials. At the end of the day, it's the outcomes that are most important to physicians and to patients.

In September, the results of the DREAM trial were presented at the European Association for the Study of Diabetes conference. This was a huge study, over three years and over 5,000 patients. The results showed that, as we had expected, Avandia does significantly reduce the risk of patients progressing into type 2 diabetes. Most of the key opinion leaders were extremely excited about these results, and they

feel they are very supportive of Avandia and the treatment guidelines being changed.

Of course, the prediabetic market is not all that big at this moment, but we expect over time, as the disease awareness grows, that this will increase. Perhaps more importantly, we expect that there's a halo effect around the product as these results become more fully understood. We will file to have this DREAM data added to the label during the first half of next year in both Europe and the US.

Of course, we're not going to have to wait very long for the next big study to report. This, of course, is the ADOPT trial, which is a four-year study. Again, this is a study in thousands of patients. But this is a study that is much more applicable to the current market, because these are actually type 2 diabetes patients. The results of this study will help doctors answer the question, which drug should I prescribe first?

Now, we are scheduling a GSK webcast on the same day that the results will be presented for the first time at a medical conference in South Africa, and that's on December 4th. We will have the chance to review the results and the implications for you then, as well as have an outlook for the entire Avandia and diabetes market, along with our projections for the market growth.

DREAM and ADOPT are the kinds of studies designed to show doctors how their patients will do over long periods of time, which is really what they are interested in. Long-term, thorough trials are what change doctors' opinions.

We can move on now. JP has already had a few comments on Coreg; let me just add to that. You can see the growth of Coreg continues at a very robust rate. While the patent for Coreg does expire next September, we still believe, as JP mentioned, there's a lot of room for improvement with Coreg.

As you know, Coreg's Achilles heel has been it's twice-a-day dosing. We have succeeded despite that with our CHF and post myocardial infarction markets with this handicap, but if you ask the patients, they certainly would prefer a once-daily product. In the antihypertensive market, a once-a-day regimen is almost a requirement for use.

So, as we mentioned, it was with great joy that we received the FDA approval for Coreg as a once-a-day treatment in all three of the conditions, in both CHF, post-MI and hypertension, just last Friday. We expect that this will be well-received by our CHF and post-MI patients. As you can see on the next slide, it really does open up that antihypertensive market opportunity that JP described.

Despite what your preconceived notions might be about beta blockers in hypertension, they are widely used in the treatment of hypertension, but they are generally required that they are once-a-day. I would expect that the once-a-day Coreg and hypertension will be very well-received by physicians and patients, and represents a tremendous opportunity to not extend the Coreg franchise but to grow it as well.

If you look at the next slide here, the three products that we've talked about and I called our rising stars in the past, I think they have almost elevated beyond rising stars to stars in their own right. If you look here -- and I do the quick math for you -- at GBP154 million in the quarter, these three products have a current run rate that exceeds $1 billion a year, and growing in the high double digits. Now, you know why we have been excited about these three products.

More specifically, looking at Requip, Requip contributed GBP70 million pounds for the quarter. You can see here the prescriptions for restless legs syndrome represent currently about 60% of the US sales and continues to grow very strongly. Many of you doubted the potential of this syndication, I doubted the potential of this indication, and there was a lot of debate within the Company. But clearly, our marketers knew what they were doing, and it has been a success for us.

We just filed the first of our two next-generation products with the FDA. First is the Requip CR, specifically designed for the restless legs syndrome patients, and a once-a-day version for our Parkinson's patients will be filed before year end.

Looking quickly as Boniva, you can see our market share gains have continued. This is a very big market, as you know, and we have a product with very clear differentiation. We will continue to be very aggressive in going after this market.

Lastly, if we can go to the last slide, this summarizes the near-term opportunities we have and the lunches that we're getting ready for in the US and around the world. In previous presentations, you heard a lot about these individual products, so I will try to keep my comments relatively brief.

I have already talked about Coreg CR. Allermist, to remind you, has the potential to be the first intranasal steroid proven to help with the ocular symptoms, which are very common and a very significant product for many people. We're hoping to launch this product in the second quarter of next year.

Tykerb has been filed, and we hope to get a priority review. So this launch is potentially not too far away. Of course, we continue to expect clinical data supporting Tykerb will build significantly over time.

Cervarix -- based on all the clinical data we have had, we're confident that the analysis of the 008 data will support a very strong file, and we also will be talking to regulators about requesting a priority review in the US.

Trexima -- in response to the FDA's approvable letter, will be submitted before year end. If all goes well, we should be launching the new gold standard for migraine treatments around midyear next year.

Data supporting Arixtra in acute coronary syndrome is also very strong. This is illustrated by the FDA granting it priority review. I think you all know how big a commercial opportunity Lovenox is, and Arixtra did very well against Lovenox in the ACS indication. So, this could be a sleeper for us.

A quick word on Entereg for POI. I remind you the PDUFA data is November 9th.

Lastly, the H5N1 pre-pandemic vaccine, different from the Flu Plus that JP talked about, is much more important than just a commercial opportunity. But we do expect to realize sales next year from this initiative, as you saw from the Swiss announcement earlier this month. There are some unknown variables on this, including the yield, and governments making firm commitments, so we want to give you a more detailed update on this at our year-end meeting in February.

So, with that, JP, I will turn the meeting back to you for Q&A.

JP GARNIER: Thank you, Julian. Thank you, David. Let's start with the Q&A.

OPERATOR: (OPERATOR INSTRUCTIONS). Matthew Weston, Lehman Brothers.

MATTHEW WESTON, ANALYST, LEHMAN BROTHERS: A couple of quick pipeline questions, if I can, given today's news. If we take some of the negatives first, on Cervarix, I would just like to know your reaction on Gardasil sales to date -- I think the market was quite surprised as to the magnitude of sales in Q3 -- and whether or not your delay out to filing in April of next year is really going to limit your ability to capture that early population of people that adopt vaccination quickly.

Secondly, on Redona, could you just give us some indication as what went wrong in the tox studies -- what should we be looking for?

Then, just on some of the more positive drivers within the pipeline, on pazopanib, can you just tell us whether or not you feel there's going to be any ability to file on the data that you currently have in renal cell carcinoma in Phase II, or do we have to wait for the Phase III to report? Also, any update in other tumors?

Then, quickly, on the MAGE-3 vaccine, you say you've got positive Phase II data, and Phase III will start. If I recall correctly, the interim data in Phase II showed a trend to significance that failed to hit the primary endpoint. Does this mean that we have actually hit the primary endpoint at the final analysis?

Then, the last one, ADOPT -- have you seen the data? I realize, with DREAM you didn't get it until a couple of days before the announcement. With ADOPT, is it different? Have you seen the data, and is that why you're confident as to positive results?

JP GARNIER: Well, so much for the advice to keep it to three questions.

MATTHEW WESTON: It's one. It's pipeline.

JP GARNIER: I'll try to answer. On Cervarix, no, we're not concerned. This is really a small delay, and the market potential is humongous. The sales of Gardasil so far are actually just scratching the surfaces along adoption rate in various markets. Remember, the delay only affects the US market.

This being said, we have previous experience; we launched our hepatitis B vaccine, I think, two years after the leader and took over market leadership within 18 months. I think that there's so much room for both vaccines that, once again, the success of Gardasil is good news. They are going to have to prepare the market, get reimbursement from the payers in the US. Then, we will be there when the market is a bit more mature. In the meantime, Gardasil will sell and some patients will get treated, but we're talking about a 10 to 12 years curve in terms of the growth curve. As we have seen, frankly -- again, hepatitis B is a pretty good model, if you want to compare takeoff and the time it takes to reach equilibrium.

Redona, we were in the back of the pack, and we hit a long-term tox finding. So we have to check whether that long-term tox in animals is meaningful, and is something to worry about, and that's why we voluntarily interrupted the trial to be very safe by precaution. As soon as we are done with the analysis, we will find out whether this is a program that should be restarted or not.

Pazopanib -- very exciting data. We have Phase III ongoing report in 18 months. I don't think that we can say anything about filing on the existing Phase II data, because the trial is not even over. Remember, this was an interim analysis after 12 weeks. So a little bit difficult to answer that question.

MAGE-3 -- we have very encouraging results. This was a small study in terms of statistical significance. I don't know exactly whether that's even important in the determination of the decision to go to Phase III. We look for an indication. I think that, certainly, the Phase III and the Phase II ended probably equal or better than the interim results. But I can't really answer your question, because I don't know, frankly.

Then, the ADOPT -- yes, we know about the data and we will be, as I said, giving you a chance to hear it from the scientists by connecting with this Avandia in focus day -- which, by the way, will be more than just talking about ADOPT. We are really bullish on Avandia.

We want to tell you about our vision of this market, of the DPPIV, of the, frankly, the range of forecast of Avandia. All those things are important. This is a big engine. This is not a product that is going to stall anytime soon, and we are prepared to back it up in a way that's going to be a big driver for the Company for years to come.

Clearly, ADOPT will be kind of newsworthy. That's why we thought we would put this focus on Avandia connected to ADOPT, but it's just a small part of the story. So, you will hear more about it on December 4th.

OPERATOR: Jami Rubin, Morgan Stanley. Mr. Rubin, your line is open.

Andrew Baum, Morgan Stanley.

ANDREW BAUM, ANALYST, MORGAN STANLEY: A couple of areas -- first, on your diabetes franchise and then, second, on potential areas for productivity improvements going forward. JP, you were very upbeat on the Avandia franchise just now, and yet at the same time, fairly dismissive of the impact that the [denoglitazone] suspension is going

to make. One of the key issues that occurs to me, at least, is the Avandia patent timeframe is limited. You have, in the near term, a challenge from Teva. Longer-term, the patent will expire of its own accord. You don't have a DPPIV, and from my understanding, part of the strategy was to add to DPPIV on top of the Avandia base, and that seems to be not open now.

Finally, if you look at the Avandia scripts in the US since the relaunch, they seem to have been somewhat disappointing, for reasons that are not entirely clear. So perhaps I could stop and just get a sense of how you're thinking about the franchise, in particular how you future-proof it, and then, in addition, some sense of what the issues are in the US market that are preventing a more impressive relaunch.

JP GARNIER: Just to be clear, I wasn't dismissive of the DPPIV. I just said we're going to tell you about how we see the market and their sort of intrusion into the market. So, being dismissive would be to deny their existence, or to think that they are not going to have an impact. That's not my point of view. I think they are going to be an important therapy, and I think it's going to benefit the glitazone indirectly. So we will tell you more about this in December.

Frankly, we think -- and again, I don't want to take too much of the thunder away from Avandia. But we think Avandia has legs and is going to grow, regardless. It would have been nice to have a DPPIV, but it's an independent fact from running the Avandia and Avandia family franchise. So, we don't seem to have one so far, unless we can resolve this problem -- which, again, could be a temporary setback.

Whether a combination of Avandia and DPPIV is a good thing or not -- we will comment on that as well. Of course, we don't need to have our own DPPIV to do that. But in the grand scheme of things, I think that the reality is that the DPPIV will be up and running way before our own horse is ready. We have to take that into account and be very realistic.

Finally -- that kind of covers it in terms of -- ah, the US, yes. Well, first of all, remember the growth in volume terms was about -- better than reported, certainly not 6% but more around 12%. The reason that we're kind of picking up now, but maybe at a lower rate than you expected, is simply because we have no samples. We're basically not promoting effectively this product line. We are short in samples if not absent of samples for both Avandia and Avandamet.

So, we're just getting back to normal. We haven't got back to normal on all aspects. We are selling the product. We have to put every single cycle of production on the material itself. You know that to compete in this market without samples for a chronic medicine is not something that helps you, in terms of gaining market share and picking up more than your fair share of new patients.

So, I am not concerned. I see the attitude of the physicians. They have burned by those two successive out-of-stocks. It's very embarrassing to get your patients to call you back because they need their repeat prescription and they can't find a pharmacist who delivers it.

So, we paid the price. We're going to come out of it, because the one thing that is sure from our market research is our physicians -- they love Avandia, they love Avandamet. They think Avandamet is the core medicine to be used in the treatment of diabetes.

That's not going to go away. But we have got to get our act together, and we finally did. The FDA requirement in Cidra just took us out of the game. The product was booming. Remember, the growth rate we were experiencing at the time -- there's no reason to believe we're not going to get back there. It's a completely artificial artifact that we have a slower pace now, and I will make a slight bet with you that we speed up on Avandia and Avandamet. But first, we have got to get supply situation and normalize the marketing of the brands. So, hopefully, that is going to happen and that's, I guess, all I have to say for the time being.

OPERATOR: Tim Anderson, Prudential.

PETER HO, ANALYST, PRUDENTIAL: This is Peter Ho for Tim Anderson. Three questions, please. On Cervarix, are you going to provide any potential cross-protection data in the near future?

On Redona, could you be a little more specific on the toxicity? Was it a carcinogenicity? What do you think this raises any questions in regards to the DPPIV inhibitors as a class?

Finally, on Advair, do you expect to achieve positive unit growth in the US in 2007, especially with the competing product coming to market?

JP GARNIER: I'll take the DPPIV and leave David explain the other two. It's a long-term carc finding, so we are seeing tumors in some long-term tox at a higher dose, and we just need to stop and look at what kind of tumors and whether those are meaningful or not.

At first look, it doesn't look like something -- we of course, talked to the FDA, although they didn't tell us to stop the trial. But when we talked to them, we actually asked -- well, not the FDA directly, but someone who has been at the FDA -- have you ever seen those kind of tumors somewhere else in the DPPIV? It's very imperfect information, but I would say probably not. But I can't be sure one way or the other.

In any case, we're going to have a conference once we have a better fix of exactly the extent, the [species], the range of dose and the like. But it is a long-term carc finding.

Then, back to David on the --

DAVID STOUT: Just on the Cervarix cross-protection, of course, we have -- based on our Phase II clinical trials, we were very helpful about some cross-protection data. Of course, we will be analyzing that as we look through the 008 trial, and we would expect to be reporting on that next year when that analysis is complete. But we have great hopes there.

In terms of Advair growth in the US, I was trying to do as good a job as I could to explain that. Let me take another stab at it. Right now, we're comparing this year to last year, which we are starting at about

the same point -- but last year, our growth was interrupted. We don't expect that growth to be interrupted this season. That's nothing in our crystal ball that says we shouldn't do what we had done in the four previous years, and that's [going to] continue to grow from this month or from September-October all the way through into next spring.

Added to that is we are hopeful to get the TORCH data into our label, both in the US and Europe. Just remind you, you have heard about TORCH now for some time, but our reps can't actually go out and promote with the TORCH data until we get it into our label. So, while we get excited about it early, the major impact won't be felt until later. So, we're very confident about the growth going forward. We know that the COPD indication is very big, a very big opportunity. As I mentioned, we put more sales resource behind it as well.

OPERATOR: Paul Diggle, Nomura.

PAUL DIGGLE, ANALYST, NOMURA: We haven't heard anything of late about [Altavex], which I think at one stage, we were hoping to hear that it would be approved or filed late this year. Can you update us on that, please?

JP GARNIER: Yes. The PDUFA is in December, so we will have to see. Until then, frankly, there isn't much to add.

PAUL DIGGLE: Is that a delayed PDUFA date?

JP GARNIER: The FDA actually asked for a delay. It's not that we delayed it; it's just that they were not quite ready. So, they put it to December.

OPERATOR: Alexandra Hauber, Bear Stearns.

ALEXANDRA HAUBER, ANALYST, BEAR STEARNS: First of all, on Streptorix, at the vaccine meeting last year, you said US trials would start in the second quarter. It appears that they have not started yet. Can you tell us when they start, and how that affects your plans for US filing?

Secondly, on Advair, you were phenomenally successful so for this year, particularly to get the price increases through. How do you think that the launch of Symbicort next year will affect your ability on the pricing power in the category?

The third question is on Avandia. It seems that there is an increasing body of evidence that long-time administration of TZDs actually increases bone loss quite dramatically. Are you actually measuring bone mineral density in DREAM and in ADOPT, so that we can get further clarity on that issue?

JP GARNIER: Your last statement on Avandia I would disagree with. I think that I can't answer your question whether we do measure bone loss in a long-term diabetic treatment trial; I just don't know. But we will come back to you on the side on that.

Then, I would like to pass on the Advair price sensitivity to David, and also the trials on Streptorix.

DAVID STOUT: Streptorix, I don't have any update at this time. We're still evaluating our strategies for the US filing and talking to the FDA.

On Symbicort launch and its potential impact -- just to remind everyone that we have the strongest package with Advair. We have all the indications for both COPD and asthma. We have the pediatric indication. We have the outcomes trials, and we have all the dosing strengths and both an MDI and a DPI dosage form.

A big part of the platform for Symbicort in Europe is to try to get this initial maintenance therapy and used for acute therapy. We don't think that's going to play very well, given the FDA's position on acute use of long-acting beta agonists. So, we feel very good about it. Anybody can always try to play in a pricing game, and we're just going to have to see where Symbicort comes in on price.

OPERATOR: Mark Purcell, Deutsche Bank.

MARK PURCELL, ANALYST, DEUTSCHE BANK: I just wondered if you could discuss, JP, in terms of your discussions on H5N1 flu vaccine priming, what level of coverage the various countries -- you were saying maybe some approvals by the end of this year in Europe -- what kind of level of coverage that the European countries are looking for?

Secondly, I think you discontinued a PDI contract sales force arrangement for 2007. I just wondered where we are in terms of the number of reps in the United States, [whether it's meaningful] going forward, and what this means in terms of SG&A growth, which I believe you have stated would grow slightly below inflation going forward.

Lastly, on Coreg sales, I wonder if you could split them by indication. Obviously, you have got the market share by indication. I'm wondering if you have the sales at hand as well.

DAVID STOUT: Let me go ahead and take all of these, if you want. In terms of the H5N1, the coverage in Europe, it's really right now that the Swiss were the first to come out, and they announced that they would be purchasing 8 million, which, if you do the quick calculations, that's enough for one for everybody in the country.

I think people are still evaluating their strategies, and the range goes everywhere from wait until pandemic to one dose for priming to two doses for priming and coverage, with hope for some cross-protection. So, I think these are part of the discussions that we're having ongoing, but all in all, the trend tends to be more and more to giving it to more people and more doses.

JP GARNIER: Let me just add to that. We can't be specific, but as I mentioned, some countries are at the end of their review processes. They will order, and then we will deliver in probably split doses 2007-2008 so we can stretch our capacity to fulfill orders for, let's say, the next two years. Countries realize that when they order, they can't get the material the next week; it's not a classic situation.

But there are countries in Europe, major countries, who are thinking like the Swiss, and there are countries that are not. We had an Asian

country buying a partial coverage of the country, and we expect this is going to be all over the place, because the experts in the various countries who are advising the government do not necessarily agree on the best strategy.

But everybody realizes that you need a safety net. There is no 100% safety net, but this one is as good as it gets. So, some of them want to buy it.

Now, back to David on Coreg and sales force.

DAVID STOUT: In terms of sales force numbers, depending on what you count in sales force, we're still in the 9,000 to 10,000 persons strong group, and we're constantly re-evaluating our needs there. Our competitiveness and share of voice and cutting of the PDI sales force will not have an impact on us.

In terms of Coreg sales, I don't have it broken down by sales by indication. You can probably get a pretty good, though, estimate if you just go in and look at that one side that I had presented, and look at the rough number of scripts. The post-MI and the CHF are very similar in terms of the cost of the script, and the patients are both using it chronically, and similar for hypertension.

MARK PURCELL: So, I was just being a bit lazy. Then, just in terms of SG&A growth going forward, is it still your expectation it's going to be below inflation? Obviously, you have mentioned a number of restructuring charges that are going to be made and new programs coming through. I just wondered if you could update us on your thoughts in terms of that cost line?

JP GARNIER: I think it varies in terms of the countries, but overall for the Corporation -- I've said it before -- we are growing R&D faster than SG&A. SG&A, every single quarter since the merger, has declined as a percentage of sales. So it's more of saying we want to keep SG&A below sales growth. Now, in some years, I was more specific and said we think for 2006 it's going to be inflation or below, which it turns out to be. That has more to do with the fact that we have really SG&A and legal in the same line. I think this is important, what Julian explained.

SG&A was down 1%, so really a good quarter for SG&A. Normally, we are up 2%, 3%. If you look at the first nine months, it's a better indication.

Legal was down because, frankly, 2005 was exceptionally high. I don't expect 2006 or 2007 to become -- yet to return to the 2005 level. We had many settlements. Some were in that provision. For all those reasons, there was a fairly -- I would say an outlier in terms of legal expenses. Now, legal expenses are always substantial, but they have clearly come down to a more natural equilibrium over this year, if you look at the first nine months. I think that's not a bad -- a trend. I hope I don't have to swallow those words, because there are some uncertainties on when we do those settlements. There's a lot of tactical moving parts there.

So, looking forward, we do have trials -- Tykerb launch and Cervarix launch. But frankly, we also have some products that get old and don't need to be promoted anymore to the same extent.

So, we continue to maintain our -- I wouldn't even call it a guidance, just common sense indication that not having reviewed the budget for 2007, I'm not going to risk telling you exactly what is going to happen. But the current guidance seems to me reasonable. I don't see any reason -- let me put it this way -- too suddenly have a spike in SG&A day over the coming year.

OPERATOR: Michael Leacock, ABN Amro.

MICHAEL LEACOCK, ANALYST, ABN AMRO: On Tykerb, I wondered if you could give us any update on the APHRODITE study timing and on the timing of the paclitaxel and Tykerb results.

On vaccines, I wondered if you could comment on the seasonal flu. Has your timing of delivery of doses changed this year, due to the different strains compared to last year's, and what your total flu vaccine capacity would be in doses?

JP GARNIER: Let David (multiple speakers).

DAVID STOUT: Yes, [I'll take the vaccine]. This year, I think we were all hit by the seasonal -- the strain change. It caused about a three-week delay of shipments. That's a big part, as I had mentioned earlier in my comments, when some shipments were delayed from the third quarter into the fourth quarter. A big chunk of that was the seasonal flu. Our total capacity for this year should be somewhere in the 55 million to 60 million range. Again, as you get further into the winter months, we haven't figured out what our cutoff point is just yet, but it's somewhere in that 55 million to 60 million.

I remind you, going forward, we intend to increase the capacity. Next year, we should almost be doubling our capacity in our Laval facility in 2007, and doubling our Dresden facility in 2008. This is going to give us not just additional seasonal flu capacity, but when we go to the Flu Plus, it will give us more opportunity. For the pandemic flu, it gives us opportunity.

JP GARNIER: On the question on Tykerb, the next piece of results will be, I guess, the combo trial with Taxol fourth quarter, so coming up.

Then, your question on the APHRODITE trial -- this is the adjuvant trial, which is a very big trial that is being organized with NIH. The start is toward the end of 2006, so assuming that NIH comes through, that we're also fairly close to the start of the trial.

OPERATOR: Stuart Harris, HSBC.

STUART HARRIS, ANALYST, HSBC: While we're talking about the APHRODITE trial, can we just confirm -- do we have a Tykerb monotherapy confirmed in that study? There seems to have been some confusion over the last six to eight months.

Secondly, will we get TORCH written up ahead of the formal addition to the US and European labels? Will it be written up in a peer-reviewed publication?

Finally, what is that threshold that you think clinicians would see as exciting, as regards efficacy of Avandia versus the other two arms in the ADOPT study which would cause increased adoption?

JP GARNIER: The last question I can't answer. We don't want to jeopardize publication and release. So, if we give too many hints, you know how it goes. So, sorry about that.

The trial APHRODITE, the latest version -- again, it has not been completely finalized. So I would rather stay away from this, as it could still -- again, we're not the only ones who have a say in the design. So I'll stay away.

Then, there was a question --

DAVID STOUT: TORCH -- we intend to publish TORCH as soon as we can in one of the good journals out there. So that should come before approval into our final label.

JP GARNIER: Thank you for all those interesting questions, and I wish you the best. We will see you in February, I guess, next time. Thank you very much.

OPERATOR: That does conclude your conference for today. Thank you for participating. You may all disconnect.

EXHIBIT 11

AN FNDW000020070215e328001s9
HD Q4 2006 GlaxoSmithKline plc Earnings Conference Call - Final
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DR. JEAN-PIERRE GARNIER, CEO, GLAXOSMITHKLINE: Good afternoon, everyone, and thank you for coming to the full-year results presentation for GSK. We will have the usual suspects today presenting to you. First, we will have our Chief Financial Officer, Julian Heslop, that many of you have met before and also followed by David Stout, our President of Pharmaceutical Operations. Then I'll come back and give you a sense of our positioning for the future, why we are so confident about 2007 and beyond.

So, without any further adieu, I would like Julian to come to the podium.

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Of course, we will have time for Q&A at the end of the session.

JULIAN HESLOP, CFO, GLAXOSMITHKLINE: Good afternoon. I would like to start by summarizing our strong financial performance in 2006. Turnover growth was 9%, which, when combined with tight control over SG&A costs, were the prime drivers of EPS growth of 19%. The dividend for 2006 is confirmed at GBP0.48, a 9% increase on the year.

I would now like to look in more detail at the fourth quarter. You'll see that turnover was up 9% with pharmaceuticals up 8% and consumer up 9%. Cost of goods as a percentage of turnover was 2.2 percentage points higher, reflecting higher restructuring charges and asset impairments and also the adverse impact of currency movements.

SG&A cost were level with 2005 and legal charges were some GBP50 million lower. If you strip out legal charges, SG&A costs increased only 2%, reflecting the benefit of previous restructuring programs.

R&D was up 6% for the quarter, although it was impacted by higher restructuring charges. Excluding this, costs increased by 3%. Other operating income was GBP100 million. GBP46 million of that was a mark-to-market gain on the Quest and Serevent financial instruments, which, as you know, move up and down every quarter, although generally from year to year represent a relatively small amount of the full-year total. Royalties were GBP35 million. Overall, operating profit growth was 19%.

You can see from this slide (technical difficulty) profit before tax grew 22% and was helped by lower interest charges. Net interest payable in the quarter benefited from the recognition of interest receivable for the year from recoverable tax. Earnings per share growth was 22%, and that was in line with PBT growth as lower minority interest charges and the benefit of the share buyback program compensated for the higher tax rate.

You'll see the quarter was adversely impacted by 16% hit from currency. This reflected the impact of a weaker dollar, which averaged $1.94 the quarter. If you remember, although it was $1.94 for quarter four, if you went back last year it was $1.73, so a $0.21 hit. Unfortunately, virtually every other major currency weakened against sterling in the quarter, and that drove that big impact you see there, that big adverse impact. Following up, if you went back to quarter four last year, you saw we had a pretty significant benefit in quarter four from currency.

The next slide shows, as usual, the impact of legal, restructuring costs, asset sale profits and Serevent and Quest on the quarter. In simple terms, the net difference was negligible and really played no impact on overall growth. If you look at it for the full year, you see it cost us about GBP78 million or 1% of operating profit.

It's perhaps worth noting that within that GBP340 million for the full year there's GBP205 million in respect to restructuring programs. I looked the other day; over the last three years we spent GBP450 million on restructuring programs, aimed at bringing down the overall cost base of the business.

This chart shows clearly in 2006 the progressive weakening of the dollar, which is almost a mirror image of its strengthening the previous year. If you look forward to 2007, [half of a] one prediction, which is you can never predict currency rates and any prediction will always be wrong. But at least if you start with where we are now on the dollar you can see that we will have, if it carries on like this, a hit, particularly in the first half of the year.

What we have done is redo this chart for you, which shows the impact of the dollar and the euro on our earnings per share. Very simply, for every $0.05 movement in the dollar, you see a 2% impact on EPS. So the dollar devalues against sterling by $0.05, you see a 2% hit, and the reverse is also true. For the euro it's about half that level.

If you want a crystal ball gaze, which is always terribly dangerous, and you say, let's assume the Q4 average rates were to apply to the dollar and the euro for the whole of 2007 and let's also assume that everything else was neutral, you would have a currency hit for the year of around 4%.

If we move on and look at the full year, turnover was up 9%, pharmaceuticals up 9% and consumer up 6%. Cost of goods as a percentage of turnover was very close to last year, and that small benefit you see reflects the benefit from an improved regional sales mix. SG&A costs were level with the previous year and benefited from a reduction in legal charges and also lower restructuring costs. If you exclude those, costs were up about 3% year on year. In 2007 we expect to see a further improvement in SG&A costs expressed as a percentage of turnover.

R&D costs increased 11%, although, again, was adversely impacted by restructuring. If you strip it out, it was about 8% for the year, the growth. If you look at that stripped-out number as a percentage of sales, it was around about 14.4%. My expectation for 2007 is that if you strip out restructuring charges you'll see R&D costs as a

percentage of turnover at around that 14.4% level, and I expect a much lower restructuring charge for R&D in 2007.

Our operating income, as you can see, was slightly lower than last year. It reflected lower asset sale profits, partly offset by a small increase in the Serevent and Quest profit and also partially offset by higher orders. Just as a matter of interest, if you take other operating income in total, more than one-third of it now represents royalties and milestone payments, so very good-quality now represented by over a third, and my expectation is that will grow.

Moving forward, you can see from this slide that the business continued to benefit from interest. You really don't benefit of having long-term fixed-rate debt and having floating-rate investment income so if interest rates rise, we continue to benefit. You can see that profit before tax and earnings per share are broadly the same, and for much the same reasons that applied in the quarter.

Looking forward to 2007, I expect a tax rate for the year of around 28.5%, a 1% improvement on 2006.

You can see from this slide the business generated over GBP8 billion in cash flow for the year. You will also see that the tax paid was much higher, reflecting the US tax settlement, which we did in September of the year. We have paid that all across now.

Capital expenditure was also higher, reflecting greater investment in the business but particularly in our vaccines business, which clearly, as we've said before, is growing significantly each year and does have a demand for capital investment to support that.

Dividends were higher, and share buyback were up a third, reflecting our new GBP2 billion a year policy that we announced in late October. Net debt at the end of the year was GBP2.5 billion. Looking forward, we expect an EPS growth rate for 2007 of between 8% and 10%.

Thank you very much. I would now like to hand over to David Stout.

DAVID STOUT, PRESIDENT, PHARMACEUTICAL OPERATIONS, GLAXOSMITHKLINE: Before I get into the 2006 results and product performance, what I thought I would do is do what I've done in years past and take a few slides to walk through some of the more important environmental issues that are out there right now and that you often write about. This year, as you would expect, a lot of it centers with what is going on in and around Washington D.C.

Let me start with Medicare Part D and the so-called -- the legislative efforts around removing the so-called noninterference clause. For those of you that are not familiar with what this is, our opponents want to reopen the Medicare Part D legislation and remove a clause that was put in, that was actually started by Democrats many years ago, which forbids the governments from getting in the middle of negotiations between the plan providers and the pharmaceutical companies. Of course, the industry thinks this is a very bad idea, and you would expect us to be against it.

But if you look at the next slide, we're not the only ones. In fact some of our biggest critics are also against reopening the legislation and changing it. You can see here quotes from the Washington Post and USA Today, not exactly friendly to the pharmaceutical industry, but they all believe that the system is working.

Let me talk a bit about why people don't think the legislation should be reopened. First of all, the program is working very well. More people are being covered than ever thought would sign up for the program. It's also costing the government significantly less than any forecast ever thought; and, most importantly, the cost to the patients is much lower than they thought it would be. In fact, the original estimates were that patients would be paying $35 per month for the program. In fact, in 2006 the costs to the patient were $23 per person per month, and in 2007 the numbers have just come out, and it has dropped again, to $22 a month. So we believe these are real signs that the free market system is working and that the program, in fact, is working.

Further, if you look at the polls, when you ask the people do they feel the plan is providing them useful benefit, the overwhelming majority of people are very positive about the Medicare Part D program.

So I guess you could ask why is all this noise happening, and it really comes down to the recent elections. This has become part of Nancy Pelosi's 100 hours. We have known for some time that there is an element in Washington that would like to put price controls into place. We believe that this kind of legislation is a bit of a Trojan horse. The good news is, is that the bill that was passed by the House of Representatives was passed by a margin that was not large enough to sustain a veto by the President. President Bush as indicated that he would veto any legislation that makes changes to Medicare Part D.

But I think even more importantly is if you look at what some of the comments were around the vote. The vote went as you would expect, all of the Democrats, 100%, voted for the bill along with a few dissenting Republicans. But within the Democratic Party themselves, there were many people that said they were voting for it only because they wanted, in the first hours of the new Congress, to go along with Nancy Pelosi. One congresswoman, in fact, went so far as to say I voted for it but I wanted in the record that I think the program is working and we don't need to make changes.

So I think that really there doesn't seem to be the stamina to really override it. If it comes back, we believe many of the pro-business Democrats will actually come out on our side, and we don't believe that the legislation will have any significant impact going forward.

Just to put some perspective around it though, I thought it would be useful for you to see what percentage of GSA's business is in the elderly population and what part of that is in Medicare Part D. As you can see on this slide, because of the makeup of our portfolio -- we have a lot of vaccines, we have products like Valtrex, Imitrex, Advair that don't necessarily gear themselves to an elderly population, we have a blow-industry average of our business targeted to the 65 and up population. Not everyone in this population actually is in a Medicare

Part D program. In fact, like GSK employees -- our retirees are in our own retirement program, and we just take a subsidy from the government.

If you look at the amount of our business that are actually in these kind of programs, it's about half of that 22% or, really, about 10% overall. So the exposure that we have -- and this is a positive and a negative. If there's any upside to the Medicare Part D legislation we don't share as much of the upside. If there is any downside to it, we, of course, don't share as much of the downside as well.

The secondary of legislative activity is around the whole area of importation. Of course, this, we believe, is very dangerous legislation. Really, I would like to focus on three things around importation. First of all, it's not necessary. Second of all, it will not produce savings. Third, it's not safe.

In terms of not being necessary, again, even our harshest critics are saying importation is not necessary. AARP, the Association of Retired People in the US, who have been the biggest people in the past to back importation legislation, have even come out and said their own studies show that seniors will be better off in the Medicare Part D program than they would from buying Canadian products over the Internet.

Also, though, is the whole idea around cost savings. When I sit down and I meet with many of the people on The Hill, they all say to me, well, we see parallel imports seem to work very well in Europe. I say to them, but yes, but do you recognize that no one, at the end, saves money? All of the profits are eaten up in the middle. It's the importers and it's the wholesalers who eat up all the profits. At the end the patients save very little.

The biggest reason, though, that we think importation is a bad deal is the safety issue. If you start to open up the borders, you open, first of all, to counterfeits. It would make it very difficult to secure the borders everywhere, and it will be all that much more difficult to stop counterfeits from coming in.

The other part -- it's a little bit tricky, but the FDA has very strict mandates for drugs that are sold in the US. They inspect every one of the plants that manufactures products intended for the US market. But we also manufacture in many countries according to local standards. If those products then come into the US, they will not have come from FDA-inspected plants. I think this would present a real quandary to the US and to the FDA. If they can't inspect all of our plants, then why bother inspecting half of the plants?

Recently, I had a discussion with one of the authors of the importation legislation. When I talked to him about this, he was totally unaware of it, didn't seem to comprehend what was going on, which just tells us that we have a lot of work to do. I can assure you we will be very active on The Hill.

Right now we don't see any of this legislation passing. We think it's too difficult. Any legislation that has passed in the last several years has always included language that would make sure that the Secretary of Health and Human Services assured the American public that, first, there will be savings and, second, that it would be safe.

For all the reasons that we have just told you, we don't think that any current secretary would do so.

On the regulatory front, of course, I don't think it's a big surprise to any of you. But the regulatory approvals are getting high and higher in terms of safety, in particular. Of course, there's also the necessity to re-up on PDUFA and so-called PDUFA 4 legislation. The current PDUFA act will expire in September of this year. The industry has already come to an agreement with the FDA on what needs to be in the language, and I can tell you we will be paying significantly more in the years to come in terms of getting our products reviewed. We are also providing more funding for our other activities, especially around safety.

Our biggest concern is that the deadline comes, towards passage of this legislation, that some of our opponents again will use this legislation (technical difficulty) and will start hanging all sorts of ornaments on it with language -- could be around importation, could be around other areas -- and that will then come down to some real good discussions and compromises. So I think on this area we're going to have to watch out.

But there is some hope, I think, on the regulatory front in terms of approvals. This is a report that I think flew a little bit under the radar screen; it was released around November, during the holiday season, and not many people saw it. But Senators Kennedy and Duribin and Congressman Waxman had requested a report from the GAO to look at what is going on in terms of drug development. Are companies spending more? Are new drugs being approved faster?

To no surprise, the report sort of backed what we have been saying for years -- that the hurdles are higher, we are spending more and more and productivity is declining and it's becoming harder to get products through the FDA. So I think, if the authors are read well in Congress, they will start to understand the issues that we have been getting across to them. If you want to dream a little bit, some of the recommendations in the report went so far as to even say, for innovative drugs, we should consider extending patent life.

So it is a little bit of a dream, but I do think there is some light at the end of the tunnel when even our harshest critics are getting reports back that say, perhaps we have gone just a little bit too far.

Just the last issue that I wanted to talk about because it's making a lot of news as the presidential race heats up is the coverage for the uninsured. Three states in the US -- Massachusetts, Pennsylvania and California -- have already passed legislation which would mandate insurance coverage for all the citizens. Bush has put forward a plan that would it also applicable at a federal level. And Senator Edwards, who is running for President, has announced his own program.

Just a few brief comments. In general, we think insurance is a great idea. It's good for people and it's good for the industry. Right now the uninsured, when they don't have their insurance, they wait till they are extremely sick and then they access the health-care system at the most expensive points, being the emergency rooms and the hospitals. They haven't taken the preventive care.

We think a good insurance program, including pharmaceutical coverage, will lend itself more to prevention. It plays well to our triple message of prevention, intervention and innovation and overall would be a good thing.

Specific to the proposals that are out there, they are relatively new. There's a lot of details to be worked out, and we really haven't taken a position on them. But again, overall, I think it's good news.

So enough on the environment. Let me move on to the 2006 performance, where you can see that our total sales grew 9% and despite the fact that we lost over GBP300 million due to the generic competition of Flonase in the US, we still had a great year. In fact, the US led the way with a very strong year. They absorbed the loss to Flonase, but they more than doubled their rate from 2005, where we grew 8%, to a 16% growth in 2006.

At the end of 2006, of course, we did start to see generic intrusions on Zofran and Wellbutrin XL 300 mg. So these are something that we will have to deal with throughout the 2007 year.

Moving to Europe, we had a strong 2005, but in 2006 we had generic competition to Lamictal and Imigran, Zofran. So it hampered our growth, but we were still, as we have been able to do in years past, despite these generic erosions, we still were able to grow the business 1%. That was due to tremendous contributions from vaccines, from Seretide and from Avandamet.

The good news in Europe -- if you look out, we really now have the bulk of our generics behind us. And so, for the next several years, with the introduction of some new vaccines and some other new products, we should see some good, healthy growth coming in Europe.

Our international growth was a little slower this year than past; it was 6%. We had some generic issues in our biggest international market, Canada, where the growth was only 3%. Then there's the usual issues in various countries; this year it was Turkey, the Philippines and our consumer business in China.

But also the bright spot continues to be Japan. This was the year of the biannual price decreases, so we took a 6% price increase to start the year. But, despite that, we still grew 8%. Again, just to remind you, this is without some of the key products that we have elsewhere in the world, and we're expecting to launch, this year alone, Seretide Lamictal and Requip in Japan. We have a very bright future going forward, and Japan will be a GBP1 billion plus business in 2007.

I think some of the reasons we have been able to continue to move forward despite the fact that we have had these generic hits is in the diversity of our portfolio. You can see here the breadth of it. In fact, you can probably take some of these categories and subdivide them even further. CNS is really a combination of both depression and neurological conditions. But I think the main point on the slide is the fact that when we take a hit, we can absorb it and we can continue to grow, as we did in 2006 when we lost generic Flonase.

Now, let me take a little bit closer look at some of our key growth drivers, and I will start with our biggest franchises, which are the Advair, Avandia and vaccines.

Let me start with Advair. Clearly, growth slowed in 2006 in both volume and in sales, especially in the US, although, despite that, we still grew overall 11%, which means we had added over GBP300 million of sales to the top line.

On this next slide, though, you can see one of the two biggest factors that are causing the slowing. We thought 2005 was an anomaly in terms of having a relatively warm season, but you can see it actually has continued and worsened into 2006. And as you can see from this slide, the asthma business and COPD business continued to decrease. This, remind you, is after ten years of continued growth in terms of office visits in both diseases. So this clearly makes it more difficult to grow your business. But you'll note that, despite that, we're still seeing the seasonal upswing that you typically see this time of year with Advair.

I think you also see in the slide the other reason for the slowing in growth. That is where we saw in November of 2005 we received an FDA advisory which required a negotiation and relabeling in our package insert. That, again, had a major impact and, we think, a more rapid than normal decline in the winter season of 2005 and 2006.

So I guess the big question, as we look out now for the rest of this year is what is going to happen over the next three months and what will happen into next year. So will the next three months be more like the 2005-2006 season, where we saw what we thought was an unexpected decline due to the fact that we were not able to compete adequately without a good label? Or will we return to the pattern that we saw in 2004 and 2005? I guess we will be talking more about that at the end of the first quarter.

I guess the other part of the good news is two warm seasons in a row. As we head into the next fall season it's logical or hopeful to expect that the year-on-year comparisons will be more normal. Perhaps if we return to more normal type winters, then there will be a potential upside as well.

Of course the real positive event for 2006 was the release of our TORCH study. This will be the major driver going forward of our growth over the next several years. Remember, while you have all heard about TORCH, and I have to keep reminding you, because we have talked to you more than anyone, we still have not been able to go out and talk to the doctors yet because it has not yet been published and we have nothing in our label. Now, we expect the publication to be in the next several months, and we have made files to all of the regulatory authorities around the world. We hope that we could go as far as perhaps getting a new indication.

But just if we were only to get language in the package insert, would certainly be good enough to describe the results of the study and would allow us to arm our representatives with it so they can begin to talk. So I hope by the end of the first half of this year I will be talking

to the doctors about TORCH and I will no longer be having to talk to you about it.

But just let me remind you of some of the positive quotes that have come out from people. Now, these are from the guys that know the study. These are the people that are familiar with the results. I'm particularly fond of the second quote, by Dr. [Sully], which -- who talked about only oxygen therapy and smoking cessation will have a greater impact on mortality in COPD than the results from the TORCH study. So I think that all lends very well to where we are going.

Okay. Let's move on to Avandia. You can see that Avandia sales grew 25% in 2006 with especially strong growth in Europe, where Avandamet has been doing very, very well. Since Europe is supplied from a site in Spain, they have not had the issues that we have seen in the US, where we have had the on-and-off-again supply issues.

Now, the US sales growth here of 24%, it's a little difficult to interpret because there were out-of-stocks, there were restockings, there were year-on-year comparisons. So I wouldn't look too strongly at the results themselves. But the good news is we're back in stock, there's no supply issue into the supply chain, and we are pretty much caught up, almost completely caught up, in our sample supply.

Of course, the really important news for 2006 was the release of two very important outcomes trials, DREAM, and more importantly, the ADOPT study, which you all heard about in December. Just to remind you what the results of that trial were, were I think we exceeded everyone's expectations, in some cases even our own, where we beat metformin on performance and we tied them on the cardiovascular safety. So this is a very positive study.

Our sales representatives immediately were able to take this study, because it was all done within label, and are now out promoting it into the doctors' offices. I can tell you doctors are very impressed with the results. We have two pieces of evidence that would back that up. First, this is the results of some market research that we have done with physicians. 92% of the physicians that have seen the ADOPT data in our market research said that it will have an impact on their prescribing. As I read through this slide, I realized I probably should have said a positive impact on their prescribing, because that's the very important part.

But also they saw, when we asked where they thought they would increase their prescribing, 55% said they would expect to increase their Avandamet prescribing. We'll talk a little bit more about that in a few seconds.

The second important indicator that it is working is actually in the results. If you look at a four-week rolling average of our TRX's, you can see that the growth is now coming back behind the brand. This has all happened since the publication of the TORCH trial.

In addition to the TRX's, I always like to look at the new RX data because new RX's predict TRX's in the future. In the two months since we've released the TORCH data we have grown almost a half of a market

share point. So if we could grow a half a market share point every two months for the rest of the year, I would be a very happy person.

So let me just wrap -- talk, telling you why we love Avandamet and why we think physicians have said they are going to be using more and more Avandamet. If you see the profile, it has very compelling efficacy. Most physicians, when they see a diabetic, they are not seeing the kind of people that you saw in the ADOPT trial, where we controlled for their HbA1c's to be in this 7 to 8 range. Most of the time they are seeing patients that are up at 9, 10 and 11 HbA1c's. They need more than one product to get the patients down.

On average, as you see here on the slide, 2.3% reductions in HbA1c. For patients with extremely high A1c's, the drop is closer to 4%.

I think equally important is the combination of the two eliminates many of the concerns that people have over either product alone. The product is weight neutral, so there's no weight gain that you sometimes see with Avandia alone; easy to take, it makes one pill twice a day; and it's very cost-effective, especially in the US, where people have co-pays. You have only one co-pay. The pricing that we have for Avandamet, we are pretty much giving the metformin component away at our cost.

Equally compelling were the results in terms of getting patients to goal. The ADA has had very rigid standards about where they think patients should be treated. As you can see again here, 77% of patients in our clinical trials were able to reach the ADA goals compared to metformin alone. So, again, we think Avandamet has a very bright future.

Next, our vaccine portfolio delivered over GBP1.7 billion of sales with very robust growth. Growth across all of our elements or all of our product franchises. US was especially strong, boistered by the flu franchise, where we were able to ship our FluLaval product in this year in great quantities. But also some real very interesting growth in products like Boostrix, a product that doesn't get a lot of attention but it's a tetanus/pertussis booster shot. Right now this growth in this size is only on a pediatric and adolescent indication. We're expecting an adult indication as well, moving forward.

Also Rotarix is doing very well. We're now getting orders throughout our Latin American markets, and we are starting to get a pickup in the European markets.

If you look at our key vaccine opportunities, moving forward and just to update you on where we are. First, just to let everyone know, EU, we're right on track with where we said we would be in terms of moving towards an approval in '07. We have completed the interim analysis on '008, and we will meet our file deadline that we promised you at the end of the third quarter by April of this year.

You also noted that we started a head-to-head trial in Gardasil this quarter. We want to be able to show the value of our adjuvant system, and we think we have designed a trial that can do that in fairly quick timeframe.

For Rotarix, we have been able to accelerate based on the interest of the US regulatory authorities, our filings. So we will now be filing in the US in the first half of this year for Rotarix.

Synflorix -- this is the new name for Streptorix. The EU did not like the name Streptorix. But I can tell you I actually like Synflorix better because it reflects more what the actually does. It's (technical difficulty) strep vaccine. It's actually a dual-acting vaccine; because of the carrier that we use, it works for otitis media as well as for strep. So I think the new name works well, it gives us a great platform, and our EU filing is expected by the end of this year.

We have continued to make progress on our new generation flu. Just to make sure you don't confuse, this is not to do with pre-pandemic or pandemic flu; this is our improved flu. This is for the elderly, whose immune systems tend to have deteriorated over time, and who the current seasonal flu doesn't seem to work as well. We have our Phase III data is expected by the end of this year, and we are very confident about the power of our adjuvant systems to produce a more boisterous seasonal flu.

Of course, very topical in the last few days year in the UK, our H5N1 vaccine program continues to just roll very well. We're actually making H5N1 vaccines today, as we speak. We have orders from a couple governments. We will be filling a Swiss order that we had announced a couple months ago. We have filed in the EU for our H5N1 vaccine, and we have cross-protection data that you will be seeing, and I hope you all have the chance to tune in at a conference in Hong Kong next month.

Let me move now to the second-tier franchises that we like to continue to talk about. We started talking about these six years ago as the next to super stars, and they have now in fact all become super stars in their own rights. We talk about Lamictal, Valtrex and Coreg all continue with very strong growth; over GBP750 million of sales each.

Just a few highlights -- Lamictal we received also now a grand mal seizure indication. This will be very helpful because we have a product called Lamictal XR, which is a once-a-day Lamictal for epilepsy coming out that was filed in '06 and hopefully will be approved by year end. So that gives us a good platform for launch on the Lamictal XR.

Valtrex -- we have new CDC guidelines that talk about transmission driving the growth there.

Of course, Coreg -- we are anxiously awaiting the launch, which will be coming in the first quarter of this year, of the Coreg CR. This will allow us to move out of the current uses of Coreg, which tend to be limited more to the CHF and the post MI market because of the twice-a-day dosing regimen, and it will allow us to move into the once-a-day beta blocker market and the bigger hypertension market. So very strong franchises, all doing very well.

And talk about now the Next Generation. I find it's kind of interesting, if you look at the total sales today of Requip, Avodart and Boniva, just about the same as where the three previous products I talked about were, five years ago, when we first started talking about them. And now, again, with great growth rates, Requip doing very well,

especially with the restless leg syndrome. Just to remind you, we have two new formulations that we will be -- or filed or will be filed. One is a 14-hour formulation specifically designed for the time period where restless leg syndrome is most prominent; and then a second, which is a 24-hour, for Parkinson's, which will reduce the titration schedule, which has been one of the real drawbacks to Requip in Parkinson's.

Avodart doing very well, the only 5-HT3 now being promoted in the population. Growth strong, and the real potential upside will be in the cancer prevention trial that we have ongoing, which we will be [reading on] in a couple of years.

Of course, Boniva, which is a once-a-month version -- osteoporosis product, growth over 100%. This is our share of the combination that we have with our marketing partner, Roche.

Let me just close on a couple of the new stars as we look out to 2007. I have already talked a little bit about Cervarix, Coreg CR and the H5N1. You will note here Wellbutrin XR in Europe -- this is the Wellbutrin XL product that we have had in the US that many people thought we would not be able to launch into the European markets. But we now have approvals in 21 countries. We are going through the pricing process right now. We should have launched in all countries by the end of this year. So this is a real upside for us.

We also have approvable letters on Altabax and Trexima and Entereg. The one key one in that group is the Trexima, which will be a fantastic addition to our migraine franchise. It takes everything that Imigran did, and Imitrex, and builds on it with greater and more superior efficacy and longer control for the patients.

Let me just talk about two products in a little more detail because these will be big launches for us in 2007. First is Allermist, which allows us to continue our allergy franchise that we built with Flonase. We have a real definitive story here -- quick onset, longer duration. But I think the two points that will have the most impact in the market is, first, that we expect to have labeling of efficacy in ocular symptoms, something that no other nasal steroid has. We have a new device that makes it easier to use; some patients well like it and find it simple.

We have a lot of Phase III data that is going to be presented at the Quad AI meeting this February, and we have five manuscripts that will be published throughout 2007.

Lastly, Tykerb -- of course, our breast cancer product. We are anticipating approval in the US in the first quarter. We have the PDUFA date coming up on March 13. Again, continuing to generate great data. In the first-line setting you'll see data -- brain metastases and inflammatory breast cancer, all during 2007.

We have also launched our adjuvant program. We know it's a long-term study, but it's well worthwhile. Based on the Herceptin adjuvant study program, knowing that Tykerb is an oral presentation, an oral formulation, would be the ideal product in the adjuvant setting.

Of course, we have ongoing studies in many other cancers -- head and neck, pancreatic and you can continue to read the rest of the slide.

So in closing, as I referenced earlier, in 2007 we do have some holes to fill. We have the Zofran in the US, we have the Wellbutrin XL 300 mg that is facing us now. We have another quarter or so of Flonase to flow through the system. But we believe our growth drivers are strong, our key franchises continue to grow. We have a great list of products that we will be launching in 2007, and that's what has allowed us to put the earnings guidance that we have put out today.

So with that I'm going to turn it back over to JP, who will walk you through the next steps.

DR. JEAN-PIERRE GARNIER: Thank you very much, David. I will go quickly through some of the fundamentals that we need to talk about because they explain a lot the outlook towards 2007.

Basically, there are three chapters to the book, to the GSK storybook. We have a portfolio, as you have seen, which is very diversified with many growth opportunities. We have a commitment to deliver strong financials in the good years, in the bad years. You were talking about the generic risk. Of course, we have some generic risk; we are a big company. We will always have [countdowns] going generic from time to time. But if you look at the track record, the last five years we have GBP6 billion of revenues going generic, and we grew our EPS on a compounded growth rate at 13%. That, I might add, with fairly few new products being launched. So we can do it, and we will continue to do it in the future.

Then, of course, R&D engine is key for the future to build up a more dynamic product line beyond what we already have. Not only that, you also try to take away some of the lack of predictability of R&D. We have, to a point where you'll see that we're able to do that, to some extent. So this is a very important competitive advantage, this reloadability that we wanted to talk to you about.

We have talked about the fact that the product portfolio is diversified geographically and therapeutically. We have 21 products with sales larger than GBP250 million. I think that's important. Blockbusters are great, but you don't want to end up with a big anchor at your foot, as some of our peers ended up. Therefore, it's easier to take some hits which are GBP500 million, GBP1 billion. But when you're dealing with very, very large franchise, it's more difficult.

We're very fortunate because the two biggest franchises we have -- they are not that vulnerable to generics. First of all, on Advair, there is no regulation to do an Advair copycat in the US. So what you're going to have is some generics at some point, certainly not in the near future. They will not be A/B rated; they will not be able to take away 90% of the sales over a week. So it's going to be a soft landing for Advair. By the way, notice in the legal report of the press release that we have had the combination patent for Advair reissued in the US. Second time the patent office looked at it and said this is a serious patent, which is a good sign for us. Of course, on top of that, we have all the patents related to the delivery system itself.

The other franchise is Avandia. Ironically, Avandia is being split into multiple parts -- again, a good way, frankly, to minimize generic inroads. You'll see in some of the PLE's, we're going beyond what we already have with Avandaryl and Avandamet; and we have, of course, been pretty clever at creating PLE's that extend the lifecycle of the major modules.

So our two biggest franchises are not typical go generic and lose it all kind of brands, which will help. On top of that, of course, we have many of those franchises which are growing fast and further diversifying us away from any major single product dependency.

Now, in fact, the strategy, as David explained, is to sustain the growth of Advair and Avandia. Those products -- I hear a lot about it when I go to visit you one-on-one. I'm a little surprised because, they were 40% of our growth this year. Three years ago there were 300% of our growth. Our dependence to Advair and Avandia has reduced considerably, very quickly. Why? Because we have built up other franchises which are growing very fast and picking up the slack, so to speak. You would expect, with the size of Advair, that we are not going to see 40% growth, ever; it's just mathematical, it's just the size of the product. But it doesn't matter because we have far more to propel the sales line.

Of course, the vaccines are doing very well, up 28% this year. If you look at the past history, we doubled the sales of the vaccines over the last five years, and we're going to do that again and easily, I would say, with Cervarix and a few other things over the next five years. So that's going to continue to be an important engine for our sales line, and then we have all the products mentioned by David, multiplicity of franchises, many of them with good news coming around the corner.

The new products opportunity. I think this is a very unusual situation, a pharmaceutical company is introducing five major new products in a single year plus a bunch of additional ones, which will make a big difference in 2008, 2009. Wellbutrin XL is the best antidepressant on the market; I think there's no argument about that. We're going to have the chance to launch it in Europe. We have beta exclusivity protection for 10 years, so this is going to be a big engine of growth for Europe.

Arixtra -- we have done a pilot in France to see if we can take on Lovenox where they are the strongest, and we have done extremely well. So we can't wait to get approval from the FDA of this indication so we can launch a major attack in the US. And you have heard about the other products from David.

Let me say a word about consumer. You see, we have a lot of oomph behind the sales line on the pharmaceutical side, but the consumer as well. The sales growth is good and improving -- 6% this year, 9% in the last quarter. So there is some momentum in our consumer healthcare business. It's also a very profitable business because we take full advantage of the synergies of the business infrastructure with pharmaceuticals, so we're number one. We're the most profitable consumer healthcare company in the world. Some of you would like us to sell it. Remember, if we sell it as a stand-alone, the consumer healthcare profit margin will drop like lead because they will lose all the synergies that exist. So it's artificially very, very profitable.

You would lose that advantage. The synergies are going to go away if you are a stand-alone. So the value of the enterprise as a stand-alone, in my view, is less than incorporated into the group, just simply on the cost synergies. On top of that, you get all the benefits of RX products switching and being passed on and being prolonged by our consumer healthcare enterprise.

There is going to be more good news on the sales line of consumer in the near future because of the innovation that is coming through. Lots of new and interesting products that are going to have a lot of appeal with consumers. I'll just mention the [Wytrace for aqua] first. That's going to be a big launch. You pay $700 to get this treatment at the dentist when you can do it in three days at home for $15.

Pronamel is very exciting; this is the first toothpaste that is demonstrated to work in the clinic against acid erosion.

Alli just got approved this morning. Alli is very tricky marketing but very high potential. Alli is on TV today; all the Americans want to talk about is alli. Obesity is a big deal in America, and this is the first time the FDA has said yes to a product to go OTC in that category. This is, in a way, sort of a freebie if you go on a diet. If you go on a diet and lose weight, that's great. If you go on a diet and take alli, you will lose 50% more than diet alone. So what do you have to lose?

Well, there are literally millions and millions of people who are constantly on a diet in America and soon in Europe; you just have to walk the streets. It's coming, it's invading Europe big-time. So this product has a place.

The trick is to launch it in a very responsible way, and this is really [entirely] up to the way we marketed Nicorette. Think about it; when we marketed Nicorette we're facing clients. Those clients want to quit smoking, but it's very hard to quit smoking. You are addicted to nicotine, and therefore the promise of the product can only be disappointing to them because you need willpower to quit smoking. Nicorette is not going to do it by itself.

Through clever marketing and making sure they understand this is not a panacea, that they need to work at it, we have been able to build $750 million business with a proposition that on paper didn't look too good.

This is the same thing. If you use alli in a low-fat for diet, it's a great product. If you do not stay on your diet and you pump a burger from time to time while taking alli, you are not going to have a great experience.

So, now this being said, there are people who are determined to lose weight, and they are committed and they are going to be patient. Those people are going to stay on alli a long time. Remember, this is half the strength of the prescription product. So some of the horror stories you heard about Xenical -- do not apply. Clinical trial, 9% dropout rate over six months. That's pretty encouraging. So we have a shot at this, and it's going to be great fun to launch the product.

Besides that, we just acquired CNS -- wonderful, clever company with two products. Both are doing fantastically well in the US and have not been globalized, and that is what SmithKline Beecham -- I should say, GlaxoSmithKline does best. It's globalizing brands, as we have done with the block products and the like. So we will launch those products worldwide. They are proven winners and expand, again, their sales line in this way.

Let me move on to financials. You know our story. For us operational excellence is embedded in our culture. I talked about it the first day of the merger. We don't do stop-and-go cost-saving, we don't do press conferences to announce body counts. We don't believe in that approach; we think it's bad management. We do cost savings even the good years. We do it all the time, and we do it for continuous improvement, and we do it without talking too much about it. But the results speak for themselves. We have reduced SG&A, we have reduced the entire cost infrastructure of the Company every single year.

Just to give you an example, in manufacturing we never mentioned it, but we have closed 28 sites in the last five years while the volume we're producing has gone up over 50%. So we know how to do this. It's boring. It's like cleaning up your room; you need to do it from time to time but nothing to write home about.

But we will deliver. In fact, if you have noticed, the guidance talks about improving margins. That's because we continue to take full advantage of our opportunities. The opportunities are tremendous to reduce the cost infrastructure those days. You can use standardization, standardize your processes, save lots of money.

Just an example -- we aligned our advertising agencies, picked up dozens of millions of dollars, and it's not that hard to do. Offshoring -- we have offshored financial services, and many other things. There's a lot more we can do.

Clinical trials -- remember, we were the first company to say let's have some clinical trials done in the low-cost countries. It's big savings for us. Well, last year, the count, I think, [month said] it's 40% of our new trials are done in low-cost countries. This has tremendous leverage on our R&D budget. We can do so much more with less.

Globalization -- this is the ultimate price arbitrage. I love it; you pick up the phone, you can save money. We buy so much more now out of India and China, for that reason. Or we get significant discounts of our local suppliers because they know they have got to compete.

Restructuring -- again, we don't talk about it, but we absorb roughly GBP200 million of restructuring in '06, which will have a payoff in '07. We will continue through '07, probably at a lower pace, though.

So there's plenty to come in terms of more efficiencies, more productivity, reducing the cost infrastructure. Of course, that helps our cash flow generation. This is just a story. Way back, we generated GBP5 billion in 2000, and we have increased significantly. The reason I show the cash flow generation is because of the next point, which is we have made a conscious decision we're going to return more to the

shareholder in the near future; we're very confident about the next five years. So we have doubled the buyback but we also increased the dividend. It's clearly a signal that we're going to keep paying dividends, maybe at a growth rate that is more similar to '05 than '04, '03, '02 or '01, where, frankly, we were increasing dividends very slowly. We think this is good for the investors and we certainly can afford it.

Now, with Julian as CFO we're not going to go wild, I have to tell you. And we shouldn't, because you have to have a very healthy balance sheet as a pharmaceutical company because there is always a Vioxx or [Efensin] just around the corner, and you have got to be able to face that, God forbid, if it were to happen. So we are going to do a reasonable job to repay basically all the cash we generate but not necessarily go into huge debt just to have a good buyback program.

R&D is very important, I don't have to tell you. Let me just go straight to the features of our R&D. The R&D pipeline is the result of changes we made, frankly, 7 to 10 years ago. And now you see that the late-stage, quote, pipeline is in a very good shape. If you think about it, in the last 12 months 10 new products entered Phase III. I have never seen that in the past, I can tell you; this is far more than anybody in the industry, far more -- not just a little more, far more than anybody else in the industry. That doesn't even count the PLE's.

We have a variety of products; this is not an R&D day, so I won't go through all of them. But basically we have lots of Phase III products, lots of file products.

I do want to mention the PLE's, because when I was talking about thinking ahead on diversifying Avandia so it doesn't become a big target for the generics, we are going to have Avandia [Prostatin]. We are going to have Avandamet Extra, we're going to have Avandaryl; we're going to have lots of different pieces to the puzzle. The sales of Avandia as a stand-alone product, as a proportion of the franchise, will be fairly modest.

There are lots of interest interesting things. Avandia XL, by the way -- that's the biggest commercial outcome if it goes through. It doesn't have a huge [pro] rate of success, but we did see some encouraging data in Phase II, this is for Alzheimer's. If we get through this one, I'll be a rich retiree, let me put it this way.

So we also filed some interesting compounds, and we are in very good shape in terms of this late-stage pipeline. So the late-stage pipeline is big, bigger than anybody else. That's good. You still need to add; more is better. But again, if you in-license early-stage compounds with big payments, something is wrong. You must be desperate to do that. We don't do that. What we in-license is late stage, it's past Phase II, it's in Phase III.

The human monoclonal, the CD-20 -- this is a product that is going to take on Rituxan. And because of its characteristics, we expect it to have an advantage in terms of antibody formation. Rituxan is a great molecule; don't get me wrong. But we think we can give them a real foot fight if the product comes through with everything that we have seen so far. So this is a product in phase III.

Geperione is an interesting -- it's a first -- it would be, if it succeeds. We have had, I would say, a mix of good studies and not-so-good studies, and we are in the final stage here of Phase III and to some extent been filed in Europe, I think. This product is very attractive. It's basically a unique mechanism of action for depression. It has been used in other diseases, and if it comes through it will be the first antidepressant beyond Wellbutrin with none of the side effects of the SSI's. So it's a good bet. We are going to find out very soon on this one.

Then XenoPort [5-110] -- [5-112] is a clever modified [neurotic]. But ironically, it has been developed in an indication that I think Warner-Lambert forgot about, which is RLS. And of course, in RLS, it acts in a very different way from Requip and the others. So this is quite exciting.

And then we're in Phase II in our neuropathic pain, which for me is a big payoff. That's where Neurontin was generating a lot of business.

So those are late stage in-licensing targets. We will continue to in-license late-stage products. The reason I don't in-license early compounds is because they have a 93% chance of failing if they are Phase I compounds. And yet you see big companies buy a bunch of Phase I products, so -- or companies with sole value is that they own some Phase I products. Let me ask you a question. If I was to tell you, you're going to buy this car, and there's a 93% chance that the car will never start, would you pay a lot of money for it? I would not. Yet today, because of the scarcity, the supply of late-stage compounds is so bad and so restricted, many companies are spending big bucks on early-stage pipelines, and we don't do that. And we will not do it, but we will continue to in-license late-stage if we can find them.

So altogether, we have a very healthy late-stage pipeline. This brings me to the second issue, which is it's great to have late-staged assets. But we have seen this year that some companies -- they lose a couple of late-stage assets, and you turnaround and there is not much behind it. I know the problem; we have suffered that problem in 2000/2001. We had some great Phase III compounds, and they died and it was a bit of bad blood. Then we turnaround, turned around, and there wasn't much right behind it. You can't have that; you have to have intensity and depth into your pipeline, and you have to be able to reload, reload the gun, reload the pipeline, at a very fast-pace.

How do we compare on the count to the rest of the industry? This is a very interesting study, it's a CMR study. First of all, we excluded vaccines and PLE's to make it clear. So this is really molecules. You are comparing to large companies, the Pfizers, the Mercks, the Sanofis, the seven largest companies. This is what they do. In terms of Phase II stuff, this is pretty much their statistics. This is what GSK does.

So we are able to fill the pipeline much faster than anybody else. Now, some of our molecules are multiple indications -- same with them. So I am going to show you that so you understand that some molecules are tried in three or four indications. We don't know what that proportion (technical difficulty) or the others; that's why the blue graph stays the way it is.

Now, you might be able to say, well, if you are three times faster at reloading your pipeline than your competition, that must be because you push a lot of garbage through and sacrifice quality for quantity. No, we don't. Our failure rate is similar, I would say identical, to the industry average. So there is nothing wrong in terms of quality of the compounds we pass through.

Then the next question is, well, you must have this huge late-stage pipeline. For sure, you can't focus like some other companies have got two or three compounds and they can move them faster. What about that? Well, this is a cycle time according to CMR which is calculated on phase-to-phase transitions. Again, this is information given by all the companies. You see, if anything, we are a little faster than most and we certainly don't get into a gridlock with our pipeline.

So the machine is working very well. The R&D machine is able to produce more molecules per dollar invested, produce them faster, produce them with a quality that is, I would say, average and hopefully will continue to improve over time. This is a major competitive advantage for the long run. I am excited about even this year, in terms of what is going to go into phase III. We have 15 shots at the goal. We will probably get five or six wins, the rest will bite the dust. There's a long list of pretty exciting products. Some of them are featured on this slide, but we will have to talk to you about it once they have passed the commitment to Phase III decision rather than before, because it's not that easy to guess which ones are going to make it and which ones are not.

Finally, I want to talk to you about some announcements we are making today. As you know, we love the CEDD system; it has been one of the factors that explained our higher productivity. So we are extending it, and we're announcing that we're going to double up on our anti-infective bed. Society needs new antibiotics. By the time we get through, we think there will be a story on first pages of newspapers about healthy people dying from resistant bugs and hospitals having to shut down their burn units and the like because it's really expanding, and this is a real problem. And nobody has invented new families of antibiotics, and we think we can do it. We will announce the leadership of this unit that we are taking from outside in the near future.

Anti-inflammation is at the core of many diseases, and the science is progressing very quickly in that field. So we are also going to create a CEDD on inflammation, and it will work in combination with our macrolide CEDD, which is a misnomer for our unit in Croatia because they work on macrolide, but they don't work on macrolide for antibody therapy, they work on macrolide for inflammation. They have fairly, I would say, early-stage but quickly moving program in that field.

Finally, I want to remind you we doubled up on biopharm. We are excited about domantis, and let me tell you what the story as with domantis; it's very simple. They have a technology where they can take a monoclonal and cut out the tail of the monoclonal. You know, the monoclonal is a very complex kind of molecule, and it's got this long domain, which is the tail of the compound, which has nothing to do with the efficacy but has, sometimes, the potential of creating antibodies.

Well, if you could cut this tail and still keep the efficacy, you would have the promise of replacing every single monoclonal that is on the market today with a better mousetrap. That is what domantis does. That's exactly what the technology is all about. That's why we're very glad we acquired it, and it is doubling up, basically, our effort in biopharm. As domantis comes through it's not going to be one monoclonal; it's going to be half a dozen. It will be the better Enbrel, the better Rituxan, the better everything. So this is a very exciting bet, and we will find out soon enough if the promise and the proof of concept we have seen so far holds up in late-stage clinical development.

Then finally, our set of alliance is expanding all the time. We have signed a number of deals. Basically, this is our virtual set. Most people don't have any chemists or biologists working in there; they just strike alliances and buy programs outside the Company. As you can imagine, this is a fast evolving field. We have many such alliances, and we're going to continue to expand. We have gained access to roughly 50 new pipelines in the last 18 months, and that, hopefully, will produce more products that we haven't talked about.

Finally, we want to globalize R&D. It makes sense to go where the best scientists are. Up to that point, it was mostly Europe, US and, to some extent, Japan. But lately, of course, we have planted our flag in India, where we have a chemistry center, and in Croatia in 2006. We are making an announcement today, we will open a fully integrated, full-fledged R&D center in China. This effort will start in '07, not end in '07. Clearly, it is going to take a little while. But Moncef will go there and finalize a site and the leadership selection.

Our Chinese R&D center will be stand-alone, will be autonomous, and will report all the way to the top of R&D. It will not be integrated with the rest. We want to create a little stimulation, and we think that this has many great advantages, so we're very excited about that.

I want to say one word about reputation. This is a Company that has broken lots of firsts to try to meet societal expectations, which are very high for the pharmaceutical industry, and have been disappointed in the past and created this sort of bad feeling about the industry. As you have seen in the surveys, the industry reputation is coming back at a very fast clip, and there are lots of reasons for that. We can come to that, if you wish, in the Q&A.

But I want to remind you we were the first company to issue a discount card for noninsured seniors in America. We were the first company to sell HIV drugs at cost on a not-for-profit basis in Africa and beyond. We were the first company to put all our clinical trials on the Web for maximum transparency. We were the first company to think that the world was going to need a pre-pandemic vaccine. We were the first company to sign deals with Bill Gates to create drugs for neglected diseases and diseases that affected primarily poor countries. We have 14 such agreements, and we are by far the largest company in terms of doing research with somebody else's money for diseases which are getting no help, from, normally, from for-profit organizations.

All this is starting to make an impact. People are starting to notice that GSK is not your [dad's] pharmaceutical company, that they get it,

that they can step ahead of the problem instead of just getting it thrown at them. You will still see some marketing practice lawyers-derived reputational issues in America; that's the way the American judicial system works. It shouldn't surprise anybody who is sophisticated and understands the plaintiff system in America, which, by the way, is broken completely. So I expect that. But very often those cases come from the past, and the measures we have put in place should help us to improve dramatically. We will shoot ourselves in the foot occasionally, I'm sure. But I think we are working very hard to restore a higher plane or reputation among our stakeholders, and I think that's good for everybody, including foreign investors.

We just, by the way, were informed we received the Paul Newman Prize. This is the most prestigious prize in corporate philanthropy, and I'll be going to New York Monday to pick it up. So our efforts are being noticed, and that's all good.

In summary, the reason we're confident about '07 and beyond is for the reasons we discussed today. We have commitment, we are determined to continue to produce, in the good years and the bad years, we always deliver. We have what it takes. We have the right portfolio of drugs -- not too concentrated but yet with lots of opportunities for growth. We have a tremendous R&D pipeline, and we're very confident about what you see is what you get, and it is pretty impressive. And we have pipeline that is not a stand-alone one and then nothing else.

If you think about reloadability, this is the only buffer against serendipity and losing drugs and then going through an empty cycle -- as we have. Of all the companies, we should know about this. We went through this. Never again, and this ability we have had to create a system that fill in the pipelines quickly is going to protect us against a certain element of serendipity, which is unavoidable in our industry.

So on that note, I would like now to ask my colleagues to come to the chair there -- Julian and David -- and then give you -- I think we have 15 minutes or so for questions. Please take advantage and ask questions.

UNIDENTIFIED AUDIENCE MEMBER: S&P Equity Research, [Johannesburg]. A question is regarding the Avandia family in the near-term as well as long-term. Did you actually see switching patients in Q4 in OLD market in the US from Avandia to Actos? How do you see compared to the universe of Avandia against new entrants such as DPP IV inhibitors and the GOP 1 in the coming years?

DAVID STOUT: I'm not sure I heard the first part. Switch or a switching (inaudible)? I can't tell you specifically switching patients, but just by monitoring market share we saw, prior to the fourth quarter, we had lost market share. When we were off the market, our market share was declining and it was almost entirely moving over to Actos. Since the release of the adopt data, our market share has been growing and the Actos market share has been declining.

Relative to the new entrants, it's been pretty much as we have said. [Genuvia] has been taking the share mostly from the sulfonylureas and, to a lesser extent, from metformin and not at all from the TZD's. That

is what is showing up in the prescription databases. It's also consistent with the market research has shown and what physicians said they would be doing.

ALEXANDER EVANS, ANALYST, DEUTSCHE BANK: Alexander, from Deutsche Bank. Just a couple more questions on Avandia, if I may. I just wondered if you could talk about the marketing effort going behind Avandia at the moment and what level you are at. Is there more to come, or are you at maximum marketing effort at the moment?

Also just a final question, thinking about Europe and the Avandia franchise there. Do you think that -- it always looks like European doctors have been fairly skeptical about this category -- about the TZDs's, which is why the penetration has been historically low. I was just wondering, do you think the DREAM and ADOPT data is going to change that perception? Could we see the penetration approaching that of the US?

DAVID STOUT: Relative to the marketing effort we're putting behind it, we have all guns blazing. The day that the ADOPT trial was announced, we were training our sales force on the ADOPT data. So they have in their bag, sheets, that detail the full story of the ADOPT data, so they are going full guns blazing.

Relative to Europe, as you saw on my slide earlier, the growth there is tremendously strong. It's really on the backs of Avandamet. We had a lot of skepticism, as you are correct, early days. But now, with the ADOPT data, physicians are seen seeing I still like my metformin, but I can see a physician for Avandia. That's why all the growth is going on Avandamet. Again, supply issues in Europe have been great. In the US, relative again to the first part of your question, the only area we are just not quite full on all of the strengths of the samples. But it's almost taken care of.

DR. JEAN-PIERRE GARNIER: Also in Europe what was helpful is the change in label. In some countries, France particularly, the [guard man] initially put Avandia in reserve of reserve of reserve, so we were in the last -- you couldn't use it for naive patients, you couldn't use it until you had to demonstrated that the patient did not succeed with metformin. It was kind of so restricted it was ridiculous.

But as soon as the studies came out and we could show the data, demonstrate that this was not warranted, they changed the label. That opened the gate. So there was also a regulatory hurdle -- not just the physicians' skepticism. The two were kind of connected. You can turn around and tell the physician, see, told you so. Suddenly, they are ready to try the product. So I think we have a great future, and 90% growth tells you that something is happening.

ANDREW BAUM, ANALYST, MORGAN STANLEY: Andrew Baum from Morgan Stanley. Perhaps Julian might like to give us some idea of where long-term -- and let's say in the next three, four years EBIT margins are going for the group. Particularly looking at R&D as a percentage of sales, given the very rich pipeline of drugs accumulating in Phase III, that you are going to develop that will leave R&D spend, to what extent can you actually contain that within the current budget?

Second, on Avandia, just following on from the previous questions, perhaps you could remind us of the dates and times of the patent case with Teva and also comment on the probability of what type of relabeling you may get regarding osteoporosis associated with the drug.

A final question on Coreg -- what percentage of the current user base do you expect to switch after twelve months following launching of Coreg CR?

DR. JEAN-PIERRE GARNIER: Let me take the margin issue. We don't give guidance on our margin, but it's obvious that we can improve it. As we are big enough, the incremental sales go straight to the bottom line. On top of that, if we can work -- continue to successfully reduce our infrastructure, there's no doubt we can have margin expansion.

We have had margin expansion in the worst of times, when prices were going down everywhere in the world except for the US, where they were not going up that much, where generics were picking up our most profitable franchise, we still increased margins. So I am very optimistic about margin expansion. We are not at Microsoft margin levels. This is a business that should produce, if you're successful with innovation, if you're successful with new products, extremely high margin. I have no doubt it will, if managed properly and, again, based on what we see today. Maybe you can take the Avandia?

DAVID STOUT: It was timelines on the Teva and Avandia? I don't -- August 6, there is litigation. Again, we feel very confident about the Avandia patent litigation there. Our composition of matter patents go out to 2012. I'm looking for nodding to confirm that?

DR. JEAN-PIERRE GARNIER: I think generic companies lately -- they stayed away against attacking NCE's because they've failed repeatedly to beat the NCE patents. But lately, they have attacked them when the NCE patent was combined with some further patent. That's exactly the case we have seen with Imitrex and we are going to see with Avandia.

Then, the day before the judgment, they dropped their lawsuit against [ENT], and they tried to attack the more vulnerable part of [your] patent portfolio. So I think one has to look at this in the light of the generic strategy.

DAVID STOUT: In terms of the labeling changes in Avandia, we have shared all of the data from ADOPT with them. Relative to osteoporosis specifically, we saw no difference in hip fractures, for example, in three different arms; and these were 4000 patients over five years. The fractures that are described in the database were not of an osteoporotic nature, and they were not significant [SAE's]; they were just reported as adverse events. So the FDA has all that data. And --

DR. JEAN-PIERRE GARNIER: Basically, the FDA thinks there's nothing to be said. Very often, the [unsterile] class, what you see the first two weeks it drops, and then it stays there. So nothing happens clinically. You have to be careful that you don't think this is a progressive loss of bone density or anything like this; that's not the way it happens. So that's reassuring.

DAVID STOUT: And relative to the -- there was one -- Coreg. We don't, as you know, give forecasts of conversions. But I'll remind you of what we said when we launched Wellbutrin XL, which was the standard in the industry was a 30% to 40% conversion rate. We had hoped to do better than that with Wellbutrin XL. We did over 50% in the first 12 months, and I think we have expectation to do every bit as well as Wellbutrin XL. So, without giving you guidance --

DR. JEAN-PIERRE GARNIER: With Coreg CR.

DAVID STOUT: With Coreg CR; sorry.

DR. JEAN-PIERRE GARNIER: Coreg CR is a little tricky because it goes beyond the conversion. First, you have the conversion of the CHS business; that's the existing business, from twice a day to once a day, we should get a fair share of that. But then on top of that we can attack, as David mentioned and I want to remind you, we can attack a very large market that with Coreg, the current Coreg, is just not competitive and frankly we don't even talk about it. That's the hypertension market. Because, if you want to treat hypertensive patients, once a day is mandatory. Nobody is going to prescribe a BID drug in hypertension. So we couldn't really go there with Coreg, even though it's on our label.

But we will go there with Coreg CR. We will get a full range of -- it's not going to be the low -- the patient that can be taken care of with a diuretic or an ACE. It's going to be the more resistant, severe, for instance, African-Americans in America have real problem with hypertension. Clearly, Coreg is a pretty powerful drug. There will be physicians trying it. So this is why it's tricky to even do it internally. We are not sure about the percentage of conversion because we've got this added market that is next to the conversion market and will benefit.

KEVIN WILSON, ANALYST, CITIGROUP : Kevin Wilson from Citigroup. On the asthma market in the US, could you tell us or share with us some of your market research on the degree of saturation it has been achieved so far in that ten years of growing it? And then comment, perhaps, on what you might think might happen when a new entrant enters the market at midyear? Will the market expand? Will you lose share? Obviously, you lose some share, but how much?

Secondly, on CapEx, could you give us some sense of what the breakout was of this year's CapEx? Going forward, will you see the same sort of levels maintained? Will it drop back to more historic levels?

DAVID STOUT: I don't have all the data, Kevin, on saturation of the market. I do know, because we were running this asthma test, do you have asthma, that we were doing that in response to the fact that we know there were a lot of -- it's not undiagnosed asthma, but it's undercontrolled asthma. That is the real opportunity, and that was what we saw in the [goal] study and the concept studies, where patients could actually get control of their asthma and in fact we could get patients through Advair to be symptom-free. So that was the real message as opposed to untapped asthma potential, was getting patients more to goal.

Again, remind you that the opportunity with Advair and Seretide is beyond the asthma market; it relies more on the COPD, which is much more of a virgin territory for us.

JULIAN HESLOP: I think on CapEx you'll see the sort of current levels the next two to three years as we invest behind the vaccines business, and [it was in off] for the manufacturing area in total. Beyond that, I think we will come down to sort of more normal levels.

JO WALTON, ANALYST, LEHMAN BROTHERS: Jo Walton from Lehman. A couple of industry and a couple of financial questions. From the industry perspective, David, you talked enthusiastically about some of the things in the Medicare Part D and the low prices. Are you concerned that together with those low prices are a number of plans which are effectively giving generics only or generics only through the doughnut hole? Do you think that that could be a problem and we might actually see an even bigger switch towards starting with generics and you, as a branded company, are getting boxed into a smaller area?

The second element is to do with pricing. You have taken, I believe, headline pricing, some pretty substantial prices on Advair in the last couple of years. Do you think that that is sustainable going forwards? Do you think, in the next few years, you will be able to take two 5% price rises a year?

On the financial side, looking at your R&D investment overall, we are obviously seeing a lot of it through the GBP3.5 billion in the P&L. But increasingly, with alliances, companies are being encouraged to capitalize investment. If you were to put all of your new product investments in, how much more are we effectively seeing that now is perhaps off-balance sheet but under the old accounting standards a couple of years ago, would have been through the P&L? Is that perhaps part of the reason you are able to keep your R&D at only 14.5% of sales whilst doing more and more in your R&D?

Just a final quick product-related question. A number of us who have followed [Axo] through the years have seen Geperione before. What have you seen about Geperione that the FDA didn't see last time it rejected it?

DAVID STOUT: Let me start with the price increase. Just to remind you, the published price increases are not the price increases that we get. I think, in general in the industry you are going to see a slowing down of the price increases because of things like Medicare Part D and more people moving into plans, and more people into various health insurance schemes.

Relative to the question on the generic plans, first, to remind you what I showed on the slide, that overall to our business, Medicare Part D is only 10% of the business. The phenomenon that you're describing, and it's a good question, is that there are a lot of people that have gone for the very generic, generic plan, which is heavily oriented to generics. If you reach the doughnut hole, they will give free generics in there. That may encourage physicians for people in those plans to start with them.

Now, remember, the kind of people that sign up, often, for the cheapest plans for the people that feel they need the medicine the least. The ones that want the best medicines or that use medicines most frequently are willing to pay more upfront. So I think that's all part of it.

The other thing that I think will happen is that there are a lot of efforts underway to try to fix the doughnut hole. We would like to be able to, for example, for the poor that can't afford it, to pay for their drugs through the doughnut hole. But unfortunately, the way the law is written today patients -- when they reach that, they can't use those savings accounts towards their costs so that, when they reach the end of the doughnut hole, they would be covered again.

So there are some fixes, some interpretation to the legislation that may go through that would help us to fix the doughnut hole, which would allow people to not have to go to the bare bones generic plans.

DR. JEAN-PIERRE GARNIER: Just on the R&D, again I want to repeat it. We can grow R&D with revenues and do fine, thank you very much, even with the expanded Phase III pipeline we have. The reason is, it's very easy to save money in R&D right now. It's very easy; you switch a trial from US to Poland, you save $9000 per patient. So, compared to the past, to the way we used to do it. There are many other reasons. You talk about CRO's and sending armies of managers for clinical trials -- we do 95% electronic data capture on our trials, 95%. We save a tremendous amount of money when we do that. Our data centers are going to India -- a tremendous amount. There are savings right, left and center for anybody who is interested in operational excellence that's a lot more efficacious than anything else you can do in the Company.

We have started to do it; there's plenty of room left. Therefore, I know you always ask, are you guys going to have to increase R&D? Well, you were asking seven years ago, when we were doubling and tripling the few assets we had in our pipeline. It never happened; we have been able to form the pipeline that is three times larger than in 2000 and a lot more late-stage and therefore a lot more -- theoretically, more expensive, than what we had. But that's because, at the same time, there is a dynamic of tremendous cost savings that is available to us, which we can do without any disruption.

It's not the off-balance that explains it; we do deals, there is some off-balance. But we depreciate it, we take write-offs when a program is terminated. As you know, many of those programs don't make it. You have to fish into that lake, and sometimes you catch a fish and sometimes you catch a shoe. So I think that's pretty much the way it goes. If you want to add anything?

JULIAN HESLOP: I think it's being done consistently over a period of time. As JP said, sure, you put some of these milestones on the balance sheet; but then, [when they] finally write them off -- so they don't just stick there forever. It's only the success ones that stay there. I'd just reinforce the point.

Within R&D, Moncef and his team are making, year-by-year, significant savings. It's those savings, actually, that fund the increased programs that charge the P&L to give you that sort of very flat percentage of sales overall. So I think it is just hard-earned, that percentage.

DR. JEAN-PIERRE GARNIER: Moncef, you want to take on the Geperione study?

MONCEF SLAOUI, CHAIRMAN, RESEARCH & DEVELOPMENT, GLAXOSMITHKLINE: Yes.

DR. JEAN-PIERRE GARNIER: Let me introduce, for some if you who have not met our new head of R&D, Moncef Slaoui.

MONCEF SLAOUI: A small clarification for something that JP said in his presentation. We have 15 program decisions to go into late-stage development. It's not always start of Phase III, just to clarify for everyone.

Geperione, it's actually very simple. The FDA rejected that product that was filed already for a while, because it did not have two positive efficacy trials in depression, which is a regulatory requirement. The reason they didn't have it is because the FDA had rejected the particular trial that Fabre-Kramer had concluded was a positive trial, and the FDA concluded otherwise.

Since then they ran a second efficacy trial that came out clearly positive, and that's what's going to go to the FDA. The FDA agreed that they would take it into an advisory committee, and that will be happening in the next few weeks, the filing.

DAVID BEADLE, ANALYST, UBS: David Beadle at UBS. Just following up on [Jay's] question on Geperione, I believe Organon do get royalties if it comes to the market or they did in the original return agreement with Kramer. I just wondered, I presume that comes out of Kramer's, that you pay them rather than you paying an additional amount to Organon? If you will pardon the pun, I suppose you're breathing a little bit easier now you have got the reissued patent on Advair. I wonder if you could just comment on what that means.

DR. JEAN-PIERRE GARNIER: What happens when, and where?

DAVID BEADLE: With the reissued patent.

DR. JEAN-PIERRE GARNIER: It's a simple story. We wanted to ensure that this patent was rock solid. You know, in Europe those combination patents don't have a lot of value, they are being challenged, successfully, in most cases. But in the US environment for patents is very different. So we looked at the patent, and we rewrote it so to take into account some of the judgments that had happening, in fact, in the UK, where some aspects of the combination patent had been challenged.

We absolutely basically put an armor plate around that patent, eliminated anything that could be attacked, that could be construed as doubtful or inexact. Remember, those patents were written originally by human beings, and human being sometimes make mistakes. So this was a way to really test the system and say, yes or no is there, and inherent synergy in the combination of those two products, [and it varies], then the patent is valid.

So that's all we did. Now, when you do that you ask for reexamination of a patent so you take a chance. In fact, you risk the patent when you do it. They could have come back and said, well, now that you have made all the changes, we don't think this is a valid patent.

So this is sort of double-or-nothing, a little bit. That's what happened, and they reexamined the patent, and the patent has been reconfirmed by the patent office. That doesn't mean it won't get challenged; but when you go in front of a judge and you say, well, here's what happened, judge, this is a lot stronger defense than if this was the first review of the patent that was written 15 years ago and nobody can relate to it anymore.

DAVID STOUT: I know, on the Geperione deal, the deal is with Fabre-Kramer, and anything that they owe downstream is their responsibility.

DR. JEAN-PIERRE GARNIER: We do pay royalties to Organon, but on Arixtra, not on Geperione.

ALEXANDRA HAUBER, ANALYST, BEAR, STEARNS & CO.: Alexandra Hauber from Bear Stearns. I was hoping to get some more information on the Arixtra approvable letter. You sounded quite positive, I believe, that this can be launched this year, so we assume you don't need additional data, given that Phase III was pretty good in the setting. Is that the right interpretation?

Second question is, I noticed on the -- oh, I didn't notice on the slide for [well into] Phase III that basically [Super Adlea] wasn't on there.

UNIDENTIFIED COMPANY REPRESENTATIVE: Which one?

ALEXANDRA HAUBER: Super Adlea. I think. (multiple speakers) Are you still choosing between the two candidates of the long-acting? And when can we expect a program to go into Phase III?

Third question is just for Julian, just to remind us how we should look at these restructuring costs [for channeling] the base. Are they coming out, or is that just some ongoing thing? Or is that some savings potential for this year?

Then the final question is, could you just remind us what is going to happen in September on Coreg when the composition of matter patent expires? Because I believe you have never challenged the bunch of generics who are planning to come in? Can you still sue them then, when they are planning to launch? What is going to happen?

DR. JEAN-PIERRE GARNIER: Okay, the last one I do not want to comment on. There is obviously an adversarial relationship with the generics and Coreg. As always, we will do our best to defend. Of course, if that defense is attacked here and that is launched CR it will make it a moot point, so I'm not going to say anything.

On our Arixtra -- Moncef, do you want to comment on the FDA, whatever we --

MONCEF SLAOUI: It is not requiring further trials. We are in discussion on some statistical analysis and other -- of course, we can't predict what the outcome is but that's --

JULIAN HESLOP: Add on the restructuring costs we spend between GBP100 million and GBP200 million every year. It's just part of running our business. It drives savings for us; it will be there every year.

DR. JEAN-PIERRE GARNIER: And [Horizon] we have multiple choices this year. We are actually running more than two programs; it's a quite complicated program.

There is also -- we have not been too specific because this is really multiple options. There's also the option of doing a combination product with [Alamna]. Alamna looks pretty good, but, again, more to come as the year unfolds.

So '07 is going to be helpful as a year to clarify what exactly do we have to replace Advair and create Super-Advair or Horizon, as we call it, at GSK. Now it's too early because all the data is not out, but there are many bets ongoing and we will sort them out as '07 proceeds.

Thank you very much for your patience, and thank you for beating the weather. Some of your colleagues didn't -- preferred to stay home to watch the Web site. But we appreciate your courage. Thank you very much.

EXHIBIT 12

The CDER Handbook

Produced by:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Revised: 03/16/98

Introduction

The CDER Handbook was developed to provide a user-friendly resource on the World Wide Web for obtaining information on the Center's processes and activities of interest to regulated industry, health professionals, academia, and the general public.

The CDER Handbook is arranged according to the four major activities that the Center is involved in: New Drug Review, Generic Drug Review, Over-the-Counter Drug Review, and Post Drug Approval Activities. Two other categories, "Communicating with CDER" and "Other Topics" are included to describe the additional activities and topics of interest at the Center.

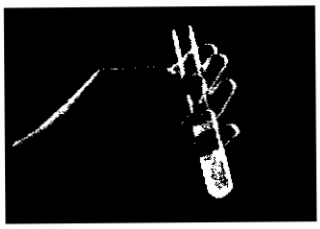
Each selection in the CDER Handbook contains a concise description of a particular process or activity and often provides resources or links to other sites for further information on a given subject.

In addition, the CDER Handbook provides an "Acronym List" to provide you with definitions of unfamiliar acronyms used in CDER. There is also a "People" section which provides links to information on how CDER is organized as well as to key points of contact within the Center.

Some documents in the CDER Handbook are in Portable Document Format (PDF) to retain the original format. To view or print these documents, you must use the Adobe Acrobat Reader. The Acrobat Reader is free and available directly from Adobe's website with full installation instructions.

The CDER Handbook was designed specifically with the Web user in mind, and it is our hope that you will find the information contained in this resource useful and easy to locate. We welcome your comments and suggestions on how this product can be improved. We hope you enjoy your visit!

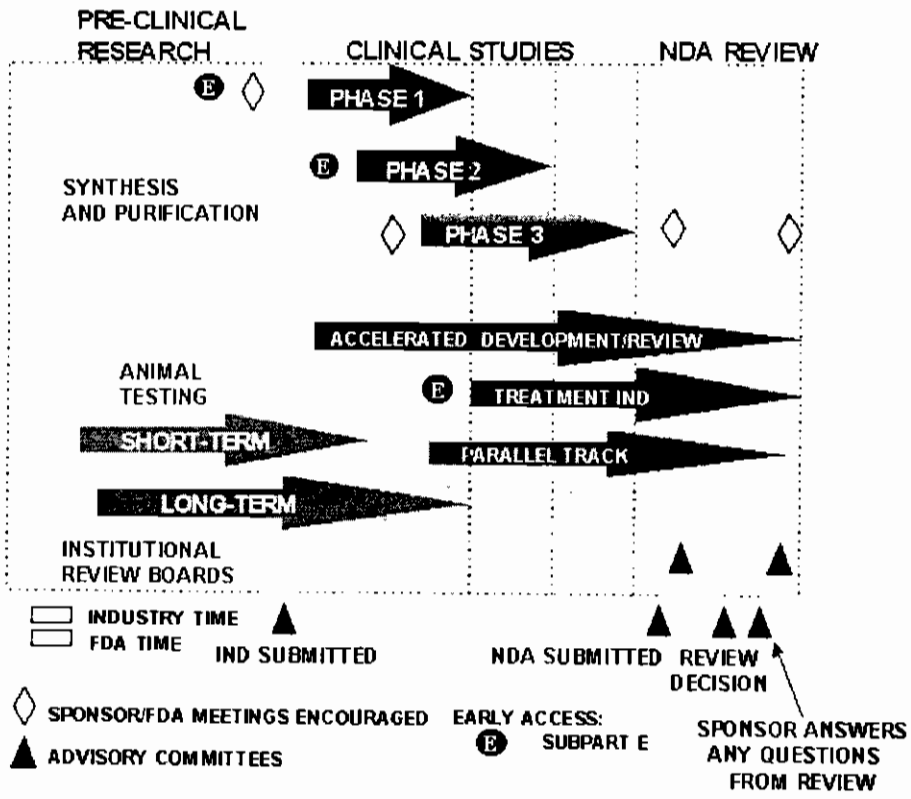
New Drug Development and Review Process



The mission of FDA's Center for Drug Evaluation and Research is to assure that safe and effective drugs are available to the American people. The information below provides an understanding of how CDER works to accomplish this mission as it relates to new drug development and review.

The New Drug Development Process:

Steps from Test Tube to New Drug Application Review



Pre-Clinical Research

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past in vitro laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

Synthesis and Purification

The research process is complicated, time-consuming, and costly and the end result is never guaranteed. Literally hundreds and sometimes thousands of chemical compounds must be made and tested in an effort to find one that can achieve a desirable result.

FDA estimates that it takes approximately eight-and-a-half years to study and test a new drug before it can be approved for the general public. This estimate includes early laboratory and animal testing, as well as later clinical trials using human subjects.

There is no standard route through which drugs are developed. A pharmaceutical company may decide to develop a new drug aimed at a specific disease or medical condition. Sometimes, scientists choose to pursue an interesting or promising line of research. In other cases, new findings from university, government, or other laboratories may point the way for drug companies to follow with their own research.

New drug research starts with an understanding of how the body functions, both normally and abnormally, at its most basic levels. The questions raised by this research help determine a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. This provides the researcher with a target. Sometimes, scientists find the right compound quickly, but usually hundreds or thousands must be screened. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which additions show some effect. This process may require testing hundreds of compounds since some may not work, but will indicate ways of

changing the compound's chemical structure to improve its performance.

Computers can be used to simulate a chemical compound and design chemical structures that might work against it. Enzymes attach to the correct site on a cell's membrane, which causes the disease. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there. But even though computers give chemists clues as to which compounds to make, a substance must still be tested within a living being.

Another approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what is known as a "fermentation broth," with one type of organism per broth. Sometimes, 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

Animal Testing

In animal testing, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Generally, two or more species (one rodent, one non-rodent) are tested because a drug may affect one species differently from another. Animal testing is used to measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of the drug and its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body.

Short-Term Testing

Short-term testing in animals ranges in duration from 2 weeks to 3 months, depending on the proposed use of the substance.

Long-Term Testing

Long-term testing in animals ranges in duration from a few weeks to several years. Some animal testing continues after human tests begin to learn whether long-term use of a drug may cause cancer or birth defects. Much of this information is submitted to FDA when a sponsor requests to proceed with human clinical trials. The FDA reviews the preclinical research data and then makes a decision as to whether to allow the clinical trials to proceed (see Clinical Studies (Overview)).

Institutional Review Boards

Institutional Review Boards (IRB) are used to ensure the rights and welfare of people participating in clinical trials both before and during their trial participation. IRBs at hospitals and research institutions throughout the country make sure that participants are fully informed and have given their written consent before studies ever begin. IRBs are monitored by the FDA to protect and ensure the safety of participants in medical research.

An IRB must be composed of no less than five experts and lay people with varying backgrounds to ensure a complete and adequate review of activities commonly conducted by research institutions. In addition to possessing the professional competence needed to review specific activities, an IRB must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. Therefore, IRBs must be composed of people whose concerns are in relevant areas.

For more information, see the *IRB Operations and Clinical Requirements* list provided by FDA's Office of Health Affairs. This document is intended to help IRB's carry out their responsibilities for protection of research subjects. Also see the March 13, 1975, Federal Register, and the Technical Amendments concerning "Protection of Human Subjects" (45 CFR Part 46).

Clinical Studies (Overview)

The new drug application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale in the United States. To obtain this authorization, a drug manufacturer submits in an NDA nonclinical (animal) and clinical (human) test data and analyses, drug information, and descriptions of manufacturing procedures.

An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including:

- Whether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks.
- Whether the drug's proposed labeling is appropriate, and, if not, what the drug's labeling should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The purpose of preclinical work--animal pharmacology/toxicology testing--is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

Although the goal of clinical trials is to obtain safety and effectiveness data, the overriding consideration in these studies is the safety of those in the trials. CDER monitors the study design and conduct of clinical trials to ensure that people in the trials are not exposed to unnecessary risks.

Subject-Related CDER Guidances of Interest

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro

Phase 1 Clinical Studies

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.

Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.

In Phase 1 studies, CDER can impose a clinical hold (i.e., prohibit the study from proceeding or stop a trial that has started) for reasons of safety, or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase 1 studies in areas other than patient safety.

Phase 2 Clinical Studies

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase 3 Clinical Studies

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate

basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

In both Phase 2 and 3, CDER can impose a clinical hold if a study is unsafe (as in Phase 1), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation.

Accelerated Development/Review

Accelerated development/review (**Federal Register, April 15, 1992**) is a highly specialized mechanism for speeding the development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses for which no therapy exists. This process incorporates several novel elements aimed at making sure that rapid development and review is balanced by safeguards to protect both the patients and the integrity of the regulatory process.

Accelerated development/review can be used under two special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when the FDA determines that safe use of a product depends on restricting its distribution or use. A surrogate endpoint is a laboratory finding or physical sign that may not be a direct measurement of how a patient feels, functions, or survives, but is still considered likely to predict therapeutic benefit for the patient.

The fundamental element of this process is that the manufacturers must continue testing after approval to demonstrate that the drug indeed provides therapeutic benefit to the patient. If not, the FDA can withdraw the product from the market more easily than usual.

Treatment IND

Treatment Investigational New Drugs (**Federal Register, May 22, 1987**) are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. In addition, these patients are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies. Treatment INDs also allow FDA to obtain additional data on the drug's safety

and effectiveness.

Parallel Track

Another mechanism to permit wider availability of experimental agents is the "parallel track" policy (***Federal Register, May 21, 1990***) developed by the U.S. Public Health Service in response to AIDS. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be promising.

Subpart E

Subpart E in ***Section 312 of the Code of Federal Regulations*** establishes procedures to expedite the development, evaluation, and marketing of new therapies intended to treat people with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternatives exist (***Federal Register, October 21, 1988***).

Sponsor/FDA Meetings (Pre-IND)

Prior to clinical studies, the sponsor needs evidence that the compound is biologically active, and both the sponsor and the FDA need data showing that the drug is reasonably safe for initial administration to humans. Under FDA requirements, the sponsor usually must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies.

Pre-clinical meetings are conducted with the appropriate review division that would review the drug marketing application and these meetings are typically requested by the sponsor of a drug. Meetings at such an early stage in the process are useful opportunities for open discussion about testing phases, data requirements, and any scientific issues that may need to be resolved prior to IND submission. At these meetings, the sponsor and FDA discuss and agree upon the design of the animal studies needed to initiate human testing. (see CFR 312.47, and CFR 312.82).

Sponsor/FDA Meetings (End of Phase 2)

The primary focus of "end of Phase 2" meetings is to determine whether it is safe to begin Phase 3 testing. This is also the time to plan protocols for Phase 3 human studies and to discuss and identify any additional information that may be required to support the submission of a new drug application. It is also intended to establish an agreement between the Agency and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. These meetings avoid unnecessary expenditures of time and money because data requirements have been clarified.

One month prior to the "end of the Phase 2" meeting, the sponsor should submit the background information and protocols for Phase 3 studies. This information should include data supporting the claim of the new drug product, chemistry data, animal data and proposed additional animal data, results of Phase 1 and 2 studies, statistical methods being used, specific protocols for Phase

3 studies, as well as a copy of the proposed labeling for a drug, if available. This summary provides the review team with information needed to prepare for a productive meeting.

Sponsor/FDA Meetings (Pre-NDA)

The purpose of a Pre-NDA meeting is to discuss the presentation of data (both paper and electronic) in support of the application. The information provided at the meeting by the sponsor includes:

- A summary of clinical studies to be submitted in the NDA;
- the proposed format for organizing the submission, including methods for presenting the data; and
- other information needed to be discussed.

The meeting is conducted to uncover any major unresolved problems or issues, to identify studies the sponsor is relying on as adequate and well controlled in establishing the effectiveness of the drug, to help the reviewers to become aquainted with the general information to be submitted and to discuss the presentation of the data in the NDA to facilitate its review.

Once the NDA is filed, a meeting may also occur 90 days after the initial submission of the application in order to discuss issues that are uncovered in the initial review.

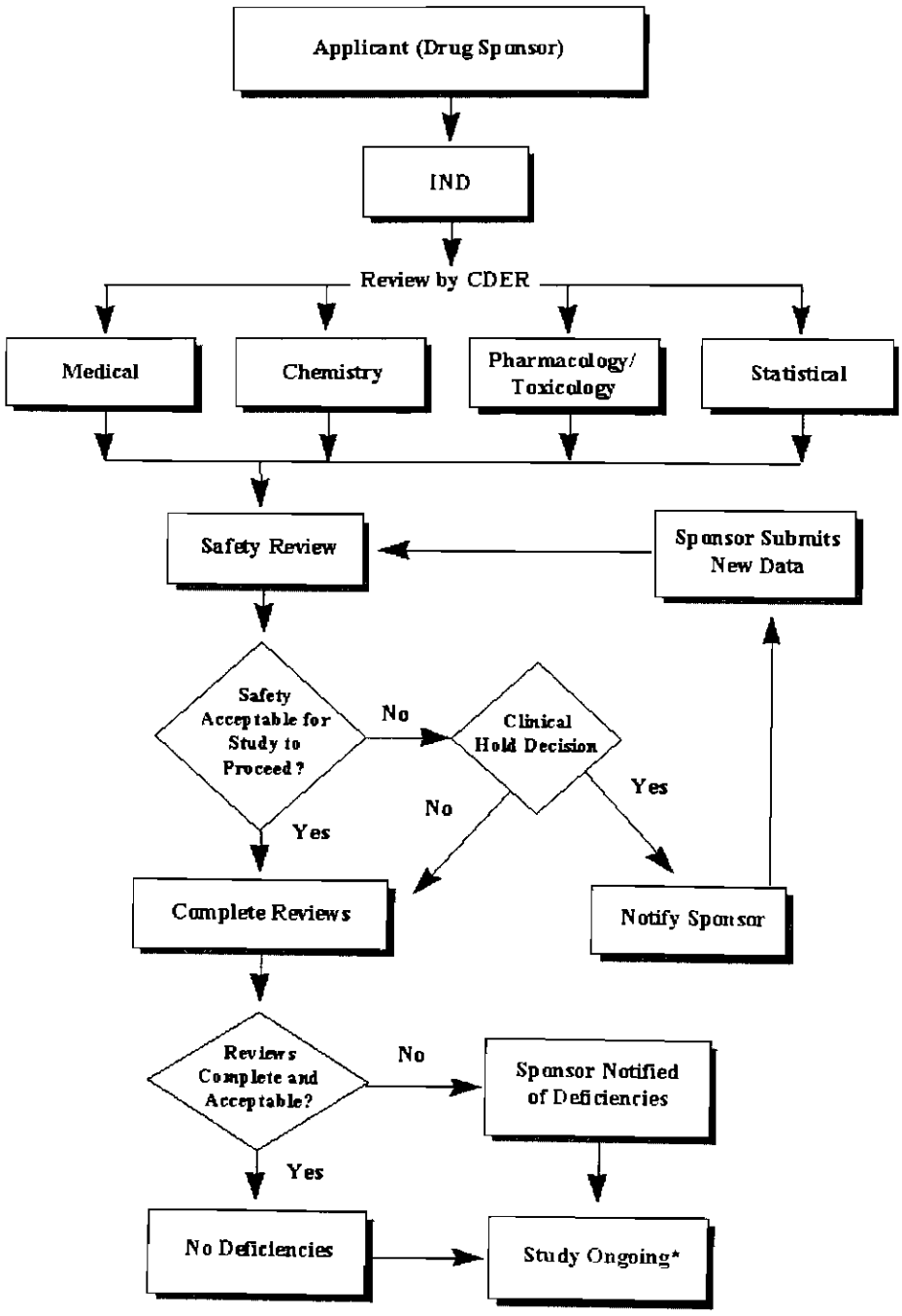
Advisory Committees

CDER uses advisory committees to obtain outside advice and opinions from expert advisors so that final agency decisions will have the benefit of wider national expert input. Committee recommendations are not binding on CDER, but the agency considers them carefully when deciding drug issues.

CDER may especially want a committee's opinion about a new drug, a major indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling. Committees may also advise CDER on necessary labeling information, or help with guidelines for developing particular kinds of drugs. They may also consider questions such as whether a proposed study for an experimental drug should be conducted or whether the safety and effectiveness information submitted for a new drug are adequate for marketing approval.

For additional information about FDA advisory committee meetings, call 1-800-741-8138. In the metropolitan Washington, D.C. area, call (301)443-0572.

IND Review Process



*While sponsor answers any deficiencies

Applicant (Drug Sponsor)

An applicant, or drug sponsor, is the person or entity who assumes responsibility for the investigation of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations. The "sponsor" is usually an individual, partnership, corporation, government agency, manufacturer or scientific institution.

Full application submissions under 21 CFR subpart 314.50 and 314.54 submitted for filing should be directed to:

Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Correspondence not associated with a particular application should be addressed specifically to the intended office or division and to the person as follows:

Center for Drug Evaluation and Research
Food and Drug Administration
Attn: [insert name of person]
HFD-[insert mail code of office or division]
5600 Fishers Lane
Rockville, MD 20857

Investigational New Drug Application

In many ways, the investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials).

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

Generally, this includes data and information in three broad areas:

- **Animal Pharmacology and Toxicology Studies**- Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
- **Manufacturing Information-** Information pertaining to the composition, manufacture,

stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed as to ensure the company can adequately produce and supply consistent batches of the drug.

- **Clinical Protocols and Investigator Information**- Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties.

The IND is not an application for marketing approval. Rather, it is a request for an exemption from the Federal statute that prohibits an unapproved drug from being shipped in interstate commerce. Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA; however, its main purpose is to detail the data that provide documentation that it is indeed reasonable to proceed with certain human trials with the drug.

Types of INDs

"Commercial INDs" are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. However, there is another class of filings broadly known as "noncommercial" INDs. The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs."

Subject-Related CDER Guidances of Interest

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
- Submitting Application Archival Copies in Electronic Format (DRAFT ONLY)
- Electronic Submission of Case Report Forms and Case Report Tabulations (DRAFT ONLY)
- Drug Master Files

Medical Review

Medical/clinical reviewers, often called medical officers, are almost exclusively physicians. In rare instances, non-physicians are used as medical officers to evaluate drug data. Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA. Within most divisions, clinical reviewers take the lead role in the IND or NDA review, and are responsible for synthesizing the results of the animal toxicology, human pharmacology and clinical reviews to formulate the overall basis for a recommended agency action on the application.

During the IND review process, the medical reviewer evaluates the clinical trial protocol to determine: (1) if the participants will be protected from unnecessary risks; and (2) if the study design will provide data relevant to the safety and effectiveness of the drug. Under Federal regulations, proposed Phase 1 studies are evaluated almost exclusively for safety reasons. Since the late 1980's, FDA reviewers have been instructed to provide drug sponsors with greater freedom during Phase 1, as long as the investigations do not expose participants to undue risks. In evaluating Phase 2 and 3 investigations, however, FDA reviewers also must ensure that these studies are of sufficient scientific quality to be capable of yielding data that can support marketing approval.

Chemistry Review

Each review division employs a team of chemists responsible for reviewing the chemistry and manufacturing control sections of drug applications. In general terms, chemistry reviewers address issues related to drug identity, manufacturing control, and analysis. The reviewing chemist evaluates the manufacturing and processing procedures for a drug to ensure that the compound is adequately reproducible and stable. If the drug is either unstable or not reproducible, then the validity of any clinical testing would be undermined because one would not know what was really being used in the patients, and, more importantly, the studies may pose significant risks to participants.

At the beginning of the Chemistry and Manufacturing section, the drug sponsor should state whether it believes the chemistry of either the drug substance or the drug product, or the manufacturing of either the drug substance or the drug product, present any signals of potential human risk. If so, these signals should be discussed, with steps proposed to monitor for such risks.

In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study. How these differences might affect the safety profile of the drug product should be discussed. If there are no differences in the products, that should be stated.

Pharmacology/ Toxicology Review

The pharmacology/toxicology review team is staffed by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential effects in humans.

Pharmacology and Drug Distribution (***21 CFR 312.23(a)(8)(I)***):

This section of the application should contain, if known: 1) a description of the pharmacologic effects and mechanism(s) of action of the drug in animals, and 2) information on the absorption, distribution, metabolism, and excretion of the drug. The regulations do not further describe the presentation of these data, in contrast to the more detailed description of how to submit toxicologic data. A summary report, without individual animal records or individual study results, usually suffices.

To the extent that such studies may be important to address safety issues, or to assist in the evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness should not generally be a reason for a Phase 1 IND to be placed on clinical hold.

Toxicology Data

Present regulations (***21 CFR 312.23(a)(8)(ii)(a)***) require an integrated summary of the toxicologic effects of the drug in animals and in vitro. The particular studies needed depend on the nature of the drug and the phase of human investigation. When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to contact the agency to discuss toxicological testing.

Subject-Related CDER Guidance of Interest

- Single Dose Acute Toxicity Testing for Pharmaceuticals
- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs

Safety Review

Following review of an initial IND submission, CDER has 30 calendar days in which to decide if a clinical hold is necessary (i.e., if patients would be at an unacceptable risk or if CDER doesn't have the data to make such a determination). Generally, drug review divisions do not contact the sponsor if no concerns arise with drug safety and the proposed clinical trials. If the sponsor hears nothing from CDER, then on day 31 after submission of the IND, the study may proceed as submitted.

Clinical Hold Decision

A clinical hold is the mechanism that CDER uses when it does not believe, or cannot confirm, that the study can be conducted without unreasonable risk to the subjects/patients. If this occurs, the Center will contact the sponsor within the 30-day initial review period to stop the clinical trial. CDER may either delay the start of an early-phase trial on the basis of information submitted in the IND, or stop an ongoing study based on a review of newly submitted clinical protocols, safety reports, protocol amendments, or other information. When a clinical hold is issued, a sponsor must address the issue that is the basis of the hold before the order is removed.

CDER's authority concerning clinical holds is outlined in Federal regulations. The regulations specify the clinical hold criteria that CDER applies to various phases of clinical testing. In addition, all clinical holds are reviewed by upper management of CDER to assure consistency and scientific quality in the Center's clinical hold decisions.

Notify Sponsor

Once a clinical hold is placed on a commercial IND, the sponsor will be notified immediately by telephone by the division director. For both individual and commercial INDs, the division is required to send a letter within five working days following the telephone call. The letter should describe the reasons for the clinical hold, and must bear the signature of the division director (or acting division director).

The sponsor may then respond to CDER by sending an "IND CLINICAL HOLD RESPONSE" letter to the division. To expedite processing, the letter must be clearly identified as an "IND CLINICAL HOLD RESPONSE" letter.

The division then reviews the sponsor's response and decides within 30 days as to whether the hold should be lifted. If the division does not reply to the clinical hold response within 30 calendar days, the division director will telephone the sponsor and discuss what is being done to facilitate completion of the review.

If it is decided that the hold will not be lifted, the hold decision is automatically sent to the office director for review. The office director must decide within 14 calendar days whether or not to sustain the division's decision to maintain the clinical hold. If the decision is made to lift the hold, the division telephones the sponsor, informs them of the decision, and sends a letter confirming that the hold has been lifted. The letter will be sent within 5 working days of the telephone call. However, the trial may begin once the decision has been relayed to the sponsor by telephone.

For more information, see MAPP 6030.1, "***IND Process and Review Procedures***".

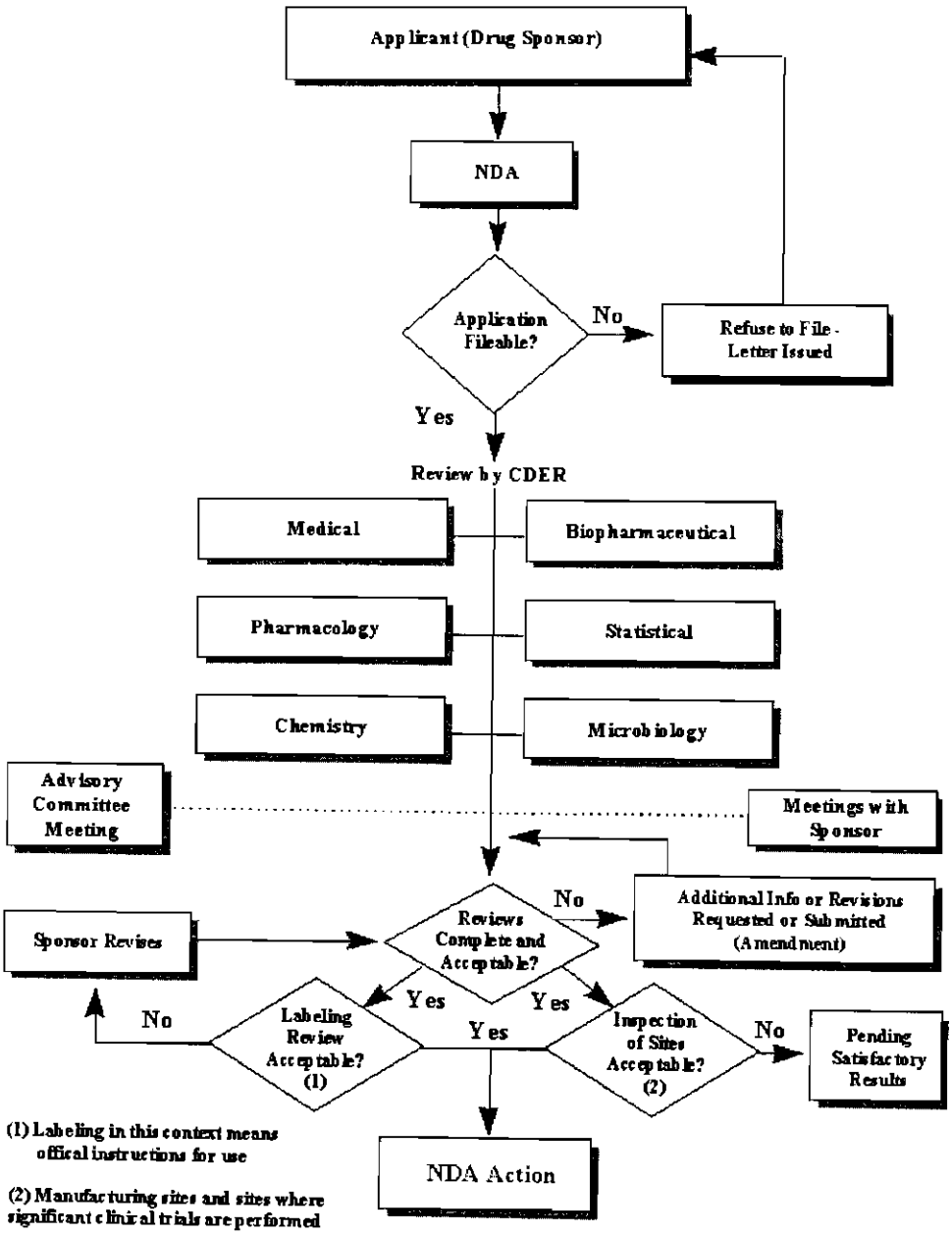
Sponsor Notified of Deficiencies

If other deficiencies are found in an IND that the review division determines are not serious enough to justify delaying clinical studies, the division may either telephone or forward a deficiency letter to the sponsor. In either case, the division informs the sponsor that it may proceed with the planned clinical trials, but that additional information is necessary to complete or correct the IND file, or that there are issues that need to be addressed prior to a marketing application (NDA) submission.

Study Ongoing

Once CDER's 30-day initial review period expires, clinical studies can be initiated, unless a clinical hold has been placed. Beyond the 30-day review period for an IND, subsequent clinical trials may begin immediately upon submission of the clinical protocol to the IND (i.e., there is no 30-day waiting period for subsequent clinical trials after the submission of the first clinical trial protocol). If the sponsor was notified of deficiencies that were not serious enough to warrant a clinical hold, the sponsor addresses these deficiencies while the study proceeds.

NDA Review Process



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Full drug marketing application submissions under 21 CFR subpart 314.50 and 314.54 should be directed to:

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Food and Drug Administration
Document and Records Section
5901-B Ammendale Rd.
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Attn: [insert name of person]
HFD-[insert mail code of office or division]
5600 Fishers Lane
Rockville, MD 20857

New Drug Application

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The NDA has evolved considerably during its history. When the Food, Drug, and Cosmetic Act (FD&C Act) was passed in 1938, NDAs were only required to contain information pertaining to the investigational drug's safety. In 1962, the Kefauver-Harris Amendments to the FD&C Act required NDAs to contain evidence that a new drug was effective for its intended use as well, and that the established benefits of the drug outweighed its known risks.

The NDA was again the subject of change in 1985, when the FDA completed a comprehensive revision of the regulations pertaining to NDAs. While this revision, commonly called the NDA Rewrite, modified content requirements, it was mainly intended to restructure the ways in which information and data are organized and presented in the NDA to expedite FDA reviews.

Fundamentals of NDA Submissions

Although the quantity of information and data submitted in NDAs can vary significantly, the components of NDAs are more uniform. The components of any NDA are, in part, a function of the nature of the subject drug and the information available to the applicant at the time of submission. As outlined in Form FDA-356h, ***Application to Market a New Drug for Human Use Or As An Antibiotic Drug For Human Use,*** NDAs can consist of as many as 15 different sections:

- Index;
- Summary;
- Chemistry, Manufacturing, and Control;
- Samples, Methods Validation Package, and Labeling;
- Nonclinical Pharmacology and Toxicology;
- Human Pharmacokinetics and Bioavailability;
- Microbiology (for anti-microbial drugs only);
- Clinical Data;
- Safety Update Report (typically submitted 120 days after the NDA's submission);
- Statistical;
- Case Report Tabulations;
- Case Report Forms;
- Patent Information;
- Patent Certification; and
- Other Information.

NDA Content and Format Requirements

Although the exact requirements are a function of the nature of a specific drug, the NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.

The FDA has numerous guidelines that relate to NDA content and format issues. These guidelines can be obtained from CDER's Drug Information Branch (DIB). Below is a partial list of some newer Guidances of interest. See DIB's Guidance Documents (at http://www.fda.gov/cder/ guidance/index.htm) for a complete list of available guidelines online and instructions on how to obtain them.

Subject-Related CDER Guidances of Interest (examples)

- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (03/97)

- Archiving Submissions in Electronic Format- NDAs (09/97)

- Drug Master Files (09/89)

NDA Classifications

CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1 through 7 are used to describe the type of drug:

1- New Molecular Entity
2- New Salt of Previously Approved Drug (not a new molecular entity)
3- New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
4- New Combination of Two or More Drugs
5- Already Marketed Drug Product - Duplication (i.e., new manufacturer)
6- New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription to OTC)
7- Already Marketed Drug Product - No Previously Approved NDA

The following letter codes describe the review priority of the drug:

S- Standard review for drugs similar to currently available drugs.
P- Priority review for drugs that represent significant advances over existing treatments.

Application Fileable?

After a New Drug Application (NDA) is received by the agency, it undergoes a technical screening generally referred to as a completeness review. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application--that is, justifying initiating CDER's formal review of the NDA.

Refuse-to-File Letter Issued

New Drug Applications that are incomplete become the subject of a formal "refuse-to-file" action. In such cases, the applicant receives a letter detailing the decision and the deficiencies that form its basis. This decision must be forwarded within 60 calendar days after the NDA is initially received by CDER.

Medical Review

Medical/clinical reviewers, often called medical officers, are almost exclusively physicians. Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA. Within most divisions, clinical reviewers take the lead role in the IND or NDA review, and are responsible for synthesizing the results of the animal toxicology, human pharmacology and clinical reviews to formulate the overall basis for a recommended Agency action on the application.

Biopharmaceutical Review

Pharmacokineticists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed in, metabolized by, and eliminated from the human body.

Statistical Review

Statisticians evaluate the statistical relevance of the data in the NDA with the main tasks of evaluating the methods used to conduct studies and the various methods used to analyze the data. The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population in the country.

Microbiology Review

The Clinical Microbiology information is required only in NDAs for anti-infective drugs. Since these drugs affect microbial, rather than human physiology, reports on the drug's in vivo and in vitro effects on the target microorganisms are critical for establishing product effectiveness.

An NDA's Microbiology section usually includes data describing:

- the biochemical basis of the drug's action on microbial physiology;
- the drug's antimicrobial spectra, including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use;
- any known mechanisms of resistance to the drug, including results of any known epidemiologic studies demonstrating prevalence of resistance factors; and
- clinical microbiology laboratory methods needed to evaluate the effective use of the drug.

More specific guidance on developing the microbiology component of the NDA is available from the FDA's ***Guideline for the Format and Content of the Microbiology Section of an Application (February 1987)***.

Advisory Committees

CDER uses advisory committees to obtain outside advice and opinions from expert advisors so that final agency decisions will have the benefit of wider national expert input. Committee recommendations are not binding on CDER, but the agency considers them carefully when deciding drug issues.

CDER may especially want a committee's opinion about a new drug, a major indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling. Committees may also advise CDER on necessary labeling information, or help with guidelines for developing particular kinds of drugs. They may also consider questions such as whether a proposed study for an experimental drug should be conducted or whether the safety and effectiveness information submitted for a new drug are adequate for marketing approval.

For additional information about FDA advisory committee meetings, call 1-800-741-8138. In the metropolitan Washington, D.C. area, call (301)443-0572.

Meetings with Sponsor

During the course of reviewing an application, CDER usually communicates often with sponsors about scientific, medical, and procedural issues that arise during the review process. Communications may take the form of telephone conversations, letters, faxes or meetings (either face-to-face or via videoconferencing).

Notification of Easily Correctable Deficiencies

CDER makes every effort to communicate promptly to applicants easily correctable deficiencies found during the review of an application. CDER also informs applicants of the need for more data or information, or for technical changes in the application needed to facilitate the agency's review. This type of early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency final decision makers as well as by reviewing staff. Instead, major scientific issues are usually addressed in an action letter at the end of the initial review process.

End of Review Conference

At the conclusion of CDER's review of an application, there are three possible action letters that can be sent to the sponsor:

- Not Approvable Letter — Lists the deficiencies in the application and explains why the application cannot be approved.
- Approvable Letter — Signals that, ultimately, the drug can be approved. Lists minor deficiencies that can be corrected, often involves labeling changes, and possibly requests commitment to do post-approval studies.
- Approval Letter — States that the drug is approved. May follow an approvable letter, but can also be issued directly.

If the action taken is either an approvable or a not approvable action (as opposed to an approval action), CDER provides applicants with an opportunity to meet with Agency officials and discuss the deficiencies. The purpose of the meeting is to discuss what further steps are necessary before the application can be approved. This meeting is available on all applications, with priority given

to applications for priority review drugs and major new indications for marketed drugs. Requests for such meetings are directed to the director of the division responsible for reviewing the application.

Other Meetings

Other meetings between CDER and applicants may be held to discuss scientific, medical, and other issues that arise during the review process. CDER makes every effort to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

For more information on meetings between CDER and applicants, see MAPP 4512.1, *"Formal Meetings Between CDER and CDER's External Constituents"*.

Reviews Complete and Acceptable?

Much of the primary review process involves reviewer attempts to confirm and validate the sponsor's conclusion that a drug is safe and effective for its proposed use. The review is likely to involve a reanalysis or an extension of the analyses performed by the sponsor and presented in the NDA. For example, the medical reviewer may seek to reanalyze a drug's effectiveness in a particular patient subpopulation not analyzed in the original submission. Similarly, the reviewer may disagree with the sponsor's assessment of evaluable patients and seek to retest effectiveness claims based on the reviewer-defined patient populations.

There is also extensive communication between review team members. If a medical reviewer's reanalysis of clinical data produces results different from those of the sponsor, for example, the reviewer is likely to forward this information to the statistical reviewer with a request for a statistical reanalysis of the data. Likewise, the pharmacology reviewer may work closely with the statistical reviewer in evaluating the statistical significance of potential cancer-causing effects of the drug in long-term animal studies.

When the technical reviews are completed, each reviewer develops a written evaluation of the NDA that presents their conclusions and their recommendations on the application. The division director or office director then evaluates the reviews and recommendations and decides the action that the division will take on the application. The result is an action letter that provides an approval, approvable or non-approvable decision and a justification for that recommendation.

Additional Information (Amendment)

In some cases, an applicant may seek to augment the information provided in the original NDA during the review process. For example, the applicant may submit a new analysis of previously submitted data, or information needed to address a deficiency in the drug application.

Any such information provided for an unapproved application is considered an NDA amendment. The submission of a significant amendment may result in an extension of FDA's time line for application review.

Labeling Review Acceptable?

Each statement proposed for drug labeling must be justified by data and results submitted in the NDA. The Code of Federal Regulations (CFR) describes labeling requirements in *21 CFR Part 201- Labeling*. The labeling is organized in the following sections:

- Description

Proprietary and established name of drug; dosage form; ingredients; chemical name; and structural formula.

- Clinical Pharmacology.

Summary of the actions of the drug in humans; in vitro and in vivo actions in animals if pertinent to human therapeutics; pharmacokinetics

- Indications and Usage

Description of use of drug in the treatment, prevention, or diagnosis of recognized disease or condition.

- Contra-Indications

Description of situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.

- Warnings

Description of serious adverse reactions and potential safety hazards, subsequent limitation in use, and steps that should be taken if they occur.

- Precautions

Information regarding any special care to be exercised for the safe and effective use of the drug. Includes general precautions and information for patients on drug interactions, carcinogenesis/mutagenesis, pregnancy rating, labor and delivery, nursing mothers, and pediatric use.

- Adverse Reactions

Description of undesirable effect(s) reasonably associated with the proper use of the drug.

- Drug Abuse/Dependence

Description of types of abuse that can occur with the drug and the averse reactions pertinent to them.

- Overdosage

Description of the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment.

- Dosage/Administration

Recommendation for usage dose, usual dosage range, and, if appropriate, upper limit beyond which safety and effectiveness have not been established.

- How Supplied

Information on the available dosage forms to which the labeling applies.

Sponsor Revises

When an NDA nears approval, agency reviewers evaluate draft package labeling for accuracy and consistency with the regulatory requirements for applicable prescription or over-the-counter drugs. Each element of the proposed labeling, including indications, use instructions, and warnings, is evaluated in terms of conclusions drawn from animal and human testing. All claims, instructions, and precautions must accurately reflect submitted clinical results.

If CDER has concerns about the draft labeling, the Center will contact the sponsor detailing suggested revisions. CDER comments can relate to almost any aspect of the proposed labeling. For example, CDER can comment upon drug indications and warnings, or suggest general changes in wording and format.

The labeling "negotiation process," through which a drug's final approved labeling is agreed upon, can take a few weeks to many months. The length of the process depends upon the number of agency comments and an applicant's willingness to reach agreement. Sometimes a sponsor will submit several revisions of labeling before agreement with FDA on the labeling can be reached.

Inspection Acceptable?

A division's decision to file an NDA begins the review process and, when needed, initiates a request for a preapproval inspection of the sponsor's manufacturing facilities and clinical trial sites. During such inspections, FDA investigators audit manufacturing-related statements and commitments made in the NDA against the sponsor's manufacturing practices. More specifically, the FDA conducts inspections to:

- verify the accuracy and completeness of the manufacturing-related information submitted in the NDA;

- evaluate the manufacturing controls for the preapproval batches upon which information provided in the NDA is based;
- evaluate the manufacturer's compliance with Current Good Manufacturing Practices (CGMPs) and manufacturing-related commitments made in the NDA; and
- collect a variety of drug samples for analysis by FDA field and CDER laboratories. These samples may be subjected to several analyses, including methods validation, methods verification, and forensic screening for substitution.

According to CDER policy, product-specific preapproval inspections generally are conducted for products: (1) that are new chemical or molecular entities; (2) that have narrow therapeutic ranges; (3) that represent the first approval for the applicant; or (4) that are sponsored by a company with a history of CGMP problems or that has not been the subject of a CGMP inspection over a considerable period. More specific guidance on CDER's preapproval inspection program is available from CDER's ***Compliance Program Guide 7346.832***.

The results of the preapproval inspection may also affect the final approval decision. When such inspections discover significant CGMP problems or other issues, the reviewing division may withhold approval until these issues are addressed and corrected. The division's response to such deficiencies is likely to depend on several factors, including the nature of the problem, the prognosis for the problem's correction, and the potential effect of the problem on the safety and efficacy of the drug.

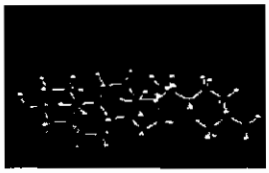
NDA Actions

Once an approval, approvable, or non-approvable recommendation is reached by the reviewers and their supervisors, the decision must be evaluated and agreed to by the director of the applicable drug review division or office. For the director's review, the consumer safety officer assembles an "action package" that contains the action letter and any data, CDER reviews and memos, and other information supporting the reviewers' recommendation.

Following his/her review of the action package, the division director may begin a dialogue with the reviewers and their supervisors. The division director generally serves as the final FDA ruling. In this sense, the division director is said to have "sign-off" authority for such drugs. The level of "sign-off" authority needed is determined by the classification of the drug under consideration. Class 1 drugs, for example, cannot be "signed off" by division directors; they require office level "sign-off" on action letters.

Once the division director (or office director, as appropriate) signs an approval action letter, the product can be legally marketed starting that day in the United States.

Generic Drug Review Process

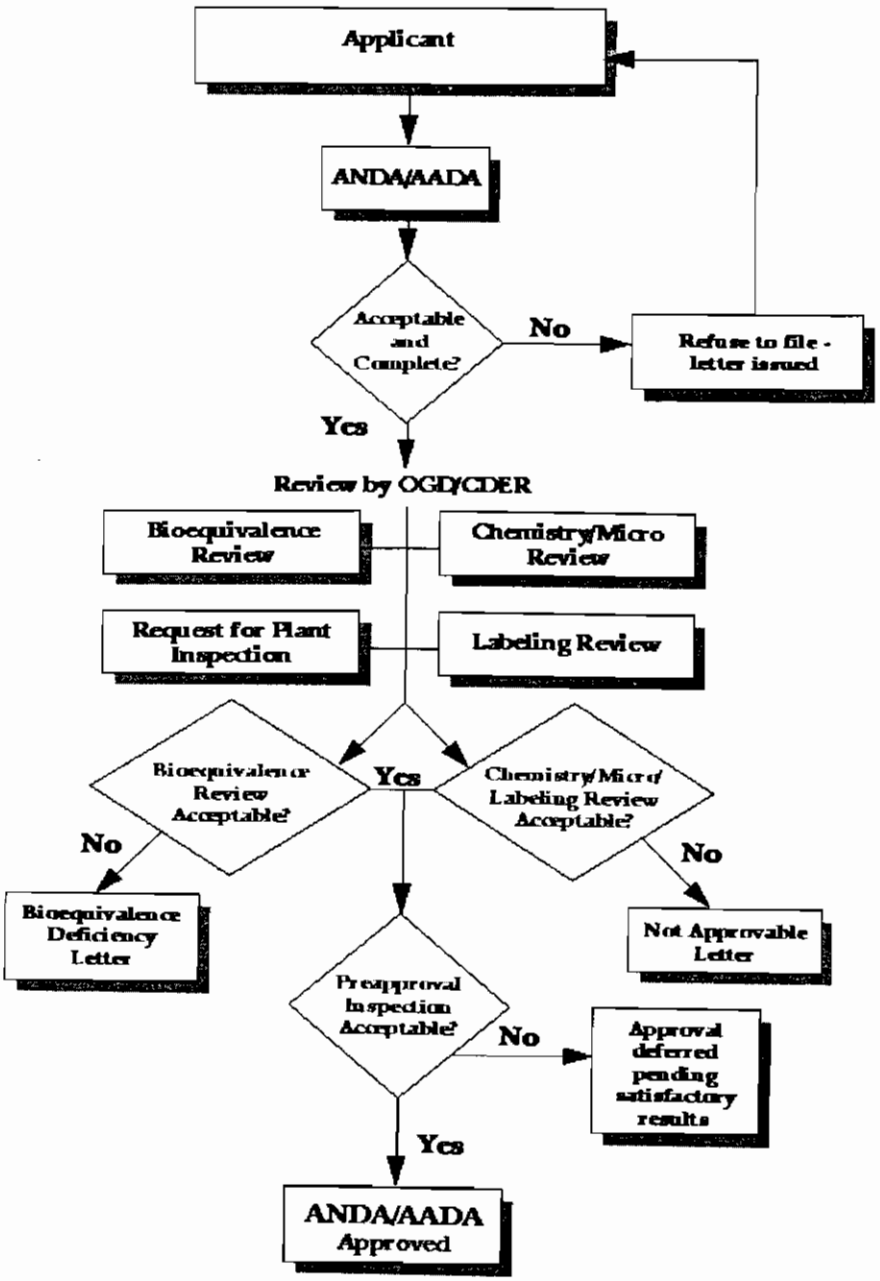


An important part of CDER's mission is to assure that safe and effective generic drugs are available to the American people. This work is accomplished in CDER's Office of Generic Drugs (OGD). The information below provides an understanding of how CDER works to assure the safety and effectiveness of generic drug products.

- Generic Drug Review Process- An interactive chart that provides an overview of CDER's abbreviated new drug application (ANDA) and abbreviated antibiotic drug application (AADA) review process, and how CDER determines the safety and bioequivalence of generic drug products prior to approval for marketing..... 30

- OGD Home Page- For further information on CDER's generic drug program, visit the Office of Generic Drugs home page at http://www.fda.gov/cder/ogd/index.htm.

Generic Drug (ANDA/AADA) Review Process



Applicant

An applicant is any person (usually a firm) who submits an abbreviated new drug application (ANDA) or an abbreviated antibiotic drug application (AADA) to obtain FDA approval to market a generic drug product and any person who owns an approved application or abbreviated application.

Abbreviated new drug applications under 21 CFR subpart 314.94, and amendments, supplements, and resubmissions; and Abbreviated antibiotic drug application submissions, as well as items sent by parcel post or overnight courier service to the Office of Generic Drugs, should be directed to:

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA/AADA

A generic drug product is one that is comparable to an innovator drug product (also known as the reference listed drug (RLD) product as identified in the FDA's ***list of Approved Drug Products with Therapeutic Equivalence Evaluations***) in dosage form, strength, route of administration, quality, performance characteristics and intended use.

Abbreviated new drug applications (ANDA's) and abbreviated antibiotic drug applications (AADA's) are submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs for review and approval. Once approved an applicant may manufacture and market the generic drug product provided all patent protection and exclusivity associated with the RLD have expired.

Generic drug applications are termed "abbreviated" in that they are not required to provide clinical data to establish safety and efficacy, since these parameters have already been established by the approval of the innovator drug product (first approved version of the drug product marketed under a brand name).

Subject-Related CDER Guidances of Interest

- Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application
- Submitting Application Archival Copies in Electronic Format (DRAFT ONLY)

• Drug Master Files

Acceptable and Complete?

An application must contain sufficient information to allow a review to be conducted in an efficient and timely manner. An initial assessment of completeness and acceptability is performed by the project manager. This initial review documents that the application contains all the necessary components and is, therefore, acceptable for filing and review.

Refuse to File Letter Issued

If the application is missing one or more essential components, a Refuse to File letter is issued to the applicant. The letter identifies the missing component(s) and informs the applicant that the application will not be filed until it is complete.

Bioequivalence Review

FDA requires an applicant to provide information to establish bioequivalency. Such information may include:

- a formulation comparison for products whose bioavailability is self evident, for example, oral solutions, injectables, or ophthalmic solutions where the formulations are identical;
- comparative dissolution testing where there is a known correlation between in vitro and in vivo effects;
- in vivo bioequivalence testing comparing the rate and extent of absorption of the generic to the reference product; and
- for non-classically absorbed products, a head-to-head evaluation of comparative effectiveness based upon clinical endpoints.

Chemistry/Microbiology Review

The Chemistry/Microbiology review provides assurance that the generic drug will be manufactured in a controlled consistent manner. Areas such as manufacturing procedures, raw material specifications and controls, sterilization processes and validation, container and closure systems, and stability are reviewed to assure that the drug will perform in an acceptable manner.

Request for Plant Inspection

Upon filing an ANDA/AADA an establishment evaluation request is forwarded to CDER's Office of Compliance to determine whether the product manufacturer, the bulk drug substance manufacturer, and any outside testing or packaging facilities are operating in compliance with current Good Manufacturing Practice regulations as outlined in *21 CFR 211*. Furthermore, a preapproval product specific inspection may be performed on certain applications to assure data integrity.

Labeling Review

The labeling review ensures that the proposed generic drug labeling is identical to that of the reference listed drug except for differences due to a change in manufacturer, patent or exclusivity issues, or if approval is based upon a suitability petition. Furthermore, the labeling review serves to identify and resolve issues of confused or mistaken identity that may arise in drug labeling in an effort to avoid drug mix-ups and prevent medication errors.

Bioequivalence Review Acceptable?

If the Bioequivalence Review determines that there are deficiencies in the Bioequivalence portion of the application, then a Bioequivalence deficiency letter is issued to the applicant. The deficiency letter will detail the deficiencies and request information and data to resolve the deficiencies. If the review determines the bioequivalence portion of the application is acceptable, a letter indicating that there are no further questions at that time will be issued.

Chemistry/Micro/Labeling Review Acceptable?

If there are deficiencies involved in the Chemistry/Manufacturing/Controls, Microbiology or Labeling portions of the application, these deficiencies are communicated to the applicant in a not approvable letter. The letter instructs the applicant to provide information and data to address the deficiencies and provides regulatory direction on how to amend their application. If the above sections are found to be acceptable, as well as the preapproval inspection and bioequivalence portion of the application, then the application moves to approval and an approval or tentative approval letter is issued.

Preapproval Inspection Acceptable?

A satisfactory recommendation from the Office of Compliance based upon an acceptable preapproval inspection is required prior to approval. If an unsatisfactory recommendation is received, a not approvable letter may be issued. In such a case, approval of the generic drug product will be deferred pending a satisfactory re-inspection and recommendation.

ANDA/AADA Approved

After all components of the application are found to be acceptable, an approval or tentative letter is issued to the applicant detailing the conditions of the approval and providing them with the ability to market the generic drug product. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the tentative approval of the generic drug product until the patent/exclusivity condition has expired. A tentative approval does not allow the applicant to market the generic drug product.

Over-the-Counter Drug Review Process

*O*ver-the-counter (OTC) drugs play an increasingly vital role in America's health care system. Today, six out of every ten medications bought by consumers are OTC drugs. Much of the work of reviewing these products is accomplished in CDER's Division of OTC Drug Products. The information below provides an understanding of how CDER works to assure the safety and efficacy of OTC drug products.

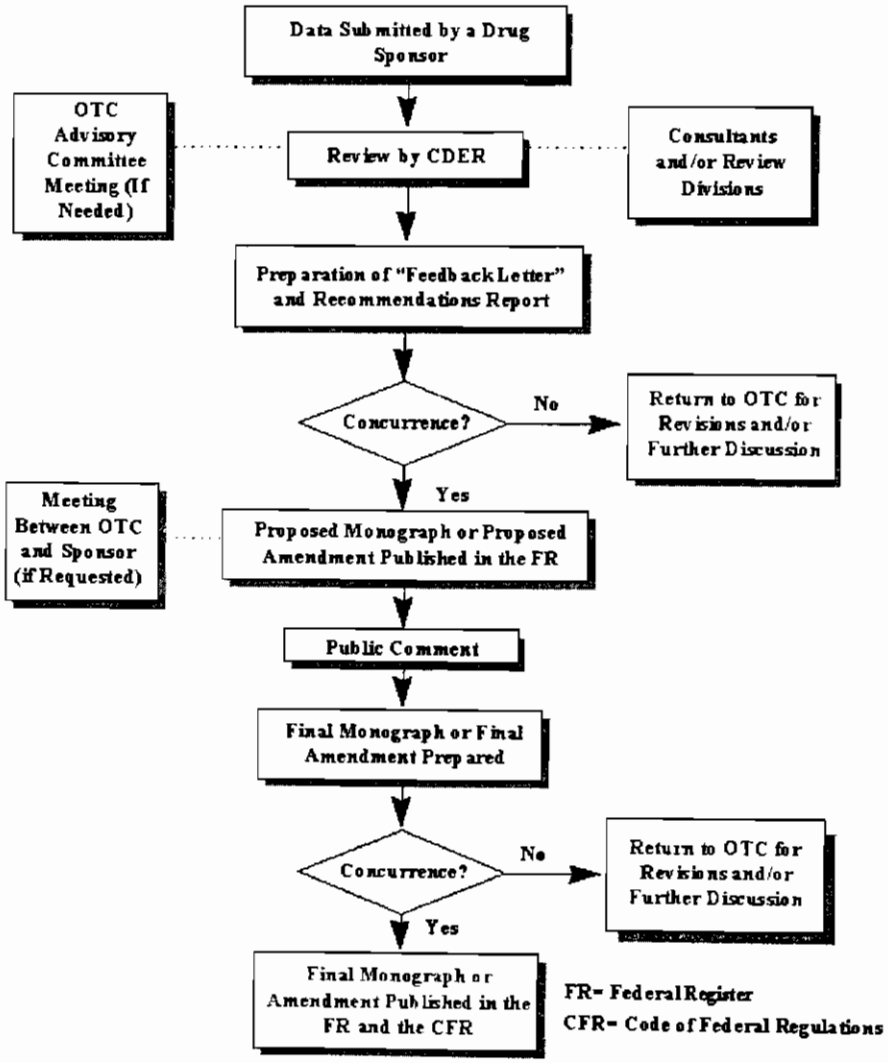
Over-the-Counter Drug Products

Over-the-Counter (OTC) drug products are those drugs that are available to consumers without a prescription. There are more than 80 classes (therapeutic categories) of OTC drugs, ranging from acne drug products to weight control drug products. As with prescription drugs, CDER oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks.

OTC drugs play an increasingly vital role in America's health care system by providing easy access to certain drugs that can be used safely without the help of a health care practitioner. This enables consumers to take control of their own health care in many situations. There are more than 100,000 OTC drug products marketed, encompassing about 800 significant active ingredients. Most OTC drug products have been marketed for many years, prior to the laws that require proof of safety and effectiveness before marketing. For this reason, FDA has been evaluating the ingredients and labeling of these products as part of "The OTC Drug Review Program." The goal of this program is to establish OTC drug monographs for each class of products. OTC drug monographs are a kind of "recipe book" covering acceptable ingredients, doses, formulations, and labeling. Monographs will continually be updated adding additional ingredients and labeling as needed. Products conforming to a monograph may be marketed without further FDA clearance, while those that do not, must undergo separate review and approval through the "New Drug Approval System." The NDA system--and not the monograph system--is also used for new ingredients entering the OTC marketplace for the first time. For example, the newer OTC products [previously available only by prescription] are first approved through the NDA system and their "switch" to OTC status is approved via the NDA system.

FDA's review of OTC drugs is primarily handled by CDER's Division of Over-the-Counter Drug Products in the Office of Drug Evaluation V. However, scientists and regulators throughout CDER, the Office of General Counsel, and other Centers within FDA are routinely asked to assist in this massive effort. There is also an advisory committee, "The Nonprescription Drug Advisory Committee," which meets regularly to assist the agency in evaluating issues surrounding these products.

OTC Drug Monograph Review Process



Data Submitted by a Drug Sponsor

Data regarding OTC monographs can be submitted by anyone- such as a drug company, health professional, consumer, or citizen's group. If the submission is a request to amend an existing drug monograph or is an opinion regarding a drug monograph, it needs to be submitted in the form of a citizen petition or as correspondence to an established monograph docket. However, if no monograph exists, data must be submitted in the format as outlined in the Code of Federal Regulations (CFR) section 330.1.

Data is submitted to the Dockets Management Branch where it is logged in and a copy is made for the public files. The data is then forwarded to the Division of Over-the-Counter Drug Products for review and action.

Review by CDER

When the package is received in the Division of OTC Drug Products, a project manager conducts an initial review to determine the type of drug being referenced and then forwards the package to the appropriate team for a more detailed review. The team leader determines if the package will need to be reviewed by other discipline areas in the review divisions, such as chemists or statisticians, or by other consultants, such as from other centers or agency offices. The package is then forwarded to a team member to review.

If the data submitted is a comment or opinion on a specific rule or monograph, there is no deadline established for CDER to respond. However, if the data is a petition or request to amend a monograph, or request to have a drug approved based on an existing monograph, the OTC division has 180 days to review the data and respond to the sponsor.

When the data is reviewed, the drug is categorized through the monograph rulemaking process as follows:

- Category I - generally recognized as safe and effective and not misbranded.
- Category II - not generally recognized as safe and effective or is misbranded.
- Category III - insufficient data available to permit classification. This category allows a manufacturer an opportunity to show that the ingredients in a product are effective, and, if they are not, to reformulate or appropriately relabel the product.

CDER also oversees OTC drug labeling because the safety and effectiveness of OTC drug products depend not only on the ingredients but also on clear and truthful labeling that can be understood by consumers.

When the initial review is complete and other consult requests have been received, a "Feedback Letter" is prepared for the sponsor outlining CDER's recommendations. The recommendations will vary depending on the type of data submitted. For example, a response based on a request to

amend a monograph may contain explanations approving or disapproving the amendment.

If the sponsor is not satisfied with the recommendations made by the division, the applicant may request a meeting to discuss any concerns.

OTC Advisory Committee Meeting

Advisory Committee meetings are usually held to discuss specific safety or efficacy concerns, or the appropriateness of a switch from prescription to OTC marketing status for a product. Usually the OTC advisory committee meets jointly with the advisory committee having specific expertise in the use of the product.

Consultants Review

Depending on the kind of data submitted, the OTC team may request that the information be reviewed by consultants from the other review divisions, i.e., chemists or statisticians; or by experts in other Centers or agency offices; or by advisory committee members (for their specific scientific expertise on a critical issue).

When the consultants complete their review of the data, their comments are returned to the OTC review team.

Preparation of "Feedback Letter"

After the OTC reviewers complete their review, a feedback letter explaining CDER's actions or recommendations will be prepared. This letter will be forwarded to the sponsor. A copy will remain on file at FDA's Dockets Management Branch.

Proposed Monograph/Amendment Published in FR

If CDER supports the recommendation of the sponsor to either amend an existing monograph or to create a new monograph, a notice is published in the Federal Register (FR). If CDER does not support the recommendation, a letter is sent to the sponsor explaining the decision to not accept the petition.

Meeting Between OTC Division and Sponsor

If the sponsor is not satisfied with the recommendations described in the feedback letter, a meeting can be requested with the division to discuss it, i.e., to provide more information, respond to any concerns of the Center, etc.

Public Comment

After the proposal is published in the Federal Register, the public has usually 30-90 days to

respond to it. This deadline depends on the controversial nature of the notice and can be extended if a request to do so is made [anyone can request an extension]. All comments are sent to the Dockets Management Branch and then are forwarded to the Division of Over-the-Counter Drug Products. The comments are reviewed/evaluated by the appropriate team and, if needed, are sent to other discipline areas for further review.

Final Monograph or Final Amendment Prepared

After the public comments have been reviewed, the final monograph is prepared. The final monograph is a kind of "recipe book" and sets final standards that specify ingredients, dosage, indications for use, and certain labeling.

Concurrence?

The final monograph is sent out for clearance through the appropriate channels, i.e., Division, Office, Center, Office of General Counsel, Deputy Commissioner for Policy, Regulations Editorial Staff.

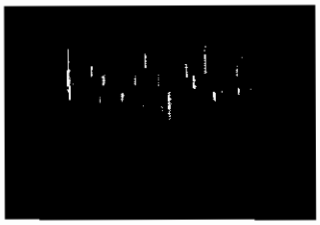
Return to OTC for Revisions/Further Discussion

If any office does not concur, the package is returned to the Division of Over-the-Counter Drug Products for revision and is then rerouted to the appropriate sources.

Final Monograph/Amendment Published in the FR and CFR

Once all revisions are made and the package receives all the appropriate final concurrences, it is published in the Federal Register (FR). All final monographs and amendments that have been published in the Federal Register are forwarded to the Regulations Editorial Staff for publication in the Code of Federal Regulations (CFR).

Post Drug Approval Activities

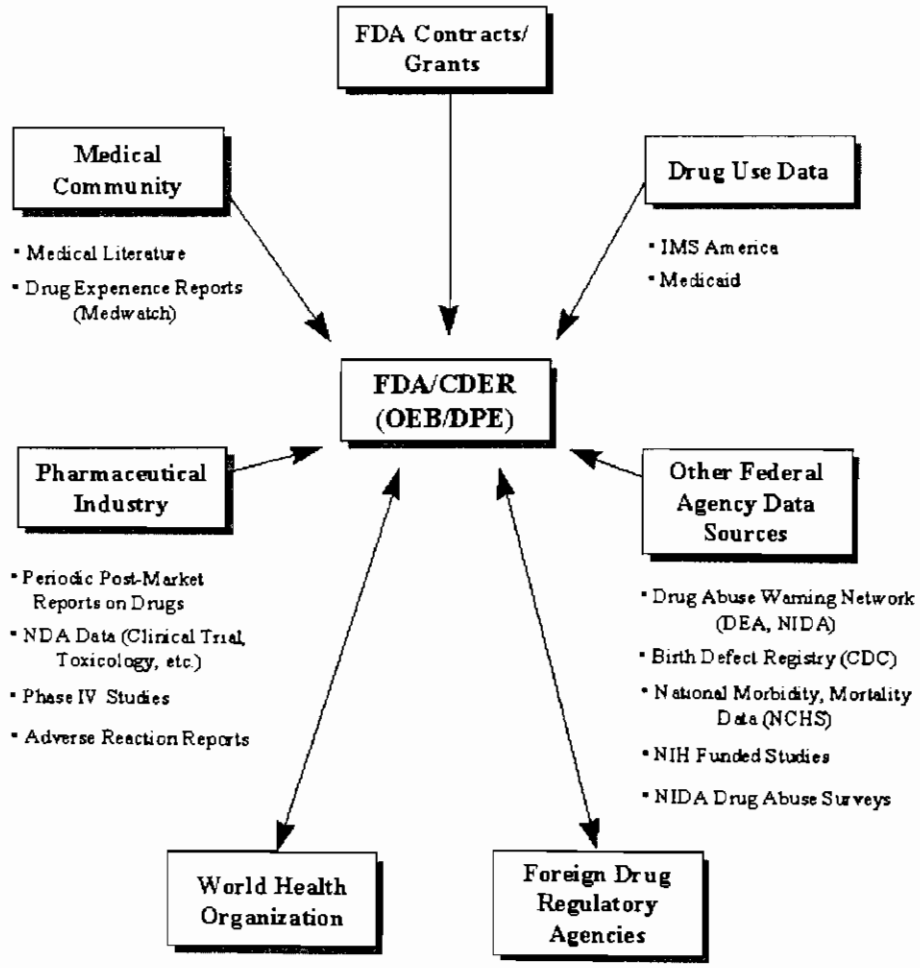


A vital part of CDER's mission is to monitor the safety and effectiveness of drugs that are currently available to the American people. The topics listed below provide an understanding of how CDER works to assure the ongoing safety and effectiveness of drug products currently marketed in the United States.

Post-Marketing Surveillance

The goal of CDER's Post-Marketing Surveillance (PMS) system is to monitor the ongoing safety of marketed drugs. This is accomplished by reassessing drug risks based on new data learned after the drug is marketed, and recommending ways of trying to most appropriately manage that risk. This is done through a variety of activities and tools that are outlined below. This work is accomplished primarily through CDER's Division of Pharmacovigilance and Epidemiology.

Drug Experience/Epidemiologic Sources Available to FDA
(For Post-Marketing Surveillance and Risk Assessment)



MEDWatch Program

Even the large, well-designed Phase 3 clinical studies that are conducted by drug manufacturers cannot uncover every problem that can come to light once a product is widely used. To capture more of this critical data, especially serious adverse event data, CDER receives expedited and periodic reports of new information from the drug's manufacturer. The manufacturers are required by regulation to make such reports. In addition, to promote and facilitate voluntary reporting of serious adverse events and product problems with drugs by health care practitioners, FDA initiated a new medical products reporting program called "MEDWatch." MEDWatch has been in effect since June 1993.

MEDWatch has four goals:

- Make it easier for healthcare providers to report serious events.
- Make it clearer to healthcare providers what types of adverse events FDA is interested in receiving.
- More widely disseminate information on the FDA's actions that have resulted from adverse event and product problem reporting.
- Increase healthcare providers' understanding and awareness of drug and device-induced disease.

The MEDWatch program makes it easy for healthcare professionals to report serious adverse events to FDA. It requires a single form that may be sent via postage-prepaid mail, fax or computer modem or uses a special call-in phone number to verbally report.

FDA is interested in learning of serious events that follow drug use. Serious events are generally defined as those that involve death, a life-threatening condition, hospitalization, disability, a congenital anomaly or intervention to one of these serious outcomes.

In return, FDA keeps healthcare professionals informed about new safety discoveries. To date, a quarterly insert in the FDA Medical Bulletin and a quarterly MEDWatch update capture the most current safety information on a routine basis. More acute information is relayed via the Internet, letters, roundtable telecon briefings with MEDWatch partners, etc.

To learn more about FDA's MEDWatch program, visit FDA's MEDWatch home page [Notice: This link will take you outside the CDER web site].

Spontaneous Reporting System

CDER's Division of Pharmacovigilance and Epidemiology (DES) maintains a Spontaneous Reporting System (SRS) which contains the adverse drug reaction reports from hospitals, health care providers and lay persons that are sent either directly to the Agency (via MEDWatch) or first to the drug manufacturer, and then, by regulation, to the Agency by the manufacturer.

In the near future, SRS will be replaced by an expanded system called the Adverse Events Reporting System (AERS), currently under development. AERS is the result of efforts to implement many agreements from the International Conference for Harmonisation (ICH) as well as new regulations and pharmacovigilance processes of the FDA to increase the efficiency with which CDER receives, files, and analyzes these reports. To learn more about AERS, visit CDER's AERS home page.

These reports are triaged through the MEDWatch program, then forwarded to the appropriate Center (Drugs, Biologics, Foods or Veterinary). Adverse Drug Reaction Reports are also sent directly from the sponsors of the New Drug Application (NDA) to the Division. When either of these types of reports are received, they are entered into the computerized SRS.

The SRS is maintained and used by DPE's data processing, epidemiology and statistic staff. Their efforts are aimed at actively analyzing the data through recognition of Adverse Drug Reaction (ADR) patterns that might indicate a public health problem (a "signal"). Improving access to the data facilitates our timely evaluation of aggregates of Adverse Drug Event (ADE) reports, which are often the first signals of a potential problem. The individual reports of serious adverse events are then critically and individually reviewed by staff trained in the analysis of these data and signal generation. DPE receives approximately 250,000 adverse experience reports possibly associated with drug use annually. Approximately 25% of the reports received by CDER are reports of serious and unlabelled (or 15-day) and/or Direct Reports.

The primary focus of DPE's reviews are to detect serious unlabeled reactions. Adverse experience reports are reviewed and analyzed to generate signals of serious, yet unrecognized, drug-associated events. These signals are communicated within DPE to staff epidemiologists and to the relevant review division via written summaries and safety conferences.

When DPE suspects that manufacturers have not been reporting ADRs as required, DPE prepares summaries of adverse drug experience reporting deficiencies and forwards this information to CDER's Office of Compliance, Division of Prescription Drug Compliance and Surveillance (DPDCS). Based on such information, DPDCS issues inspectional assignments to FDA field offices to follow-up these deficiencies at the pertinent firm. DPDCS evaluates the information provided by DPE along with the inspectional findings and makes a determination if further regulatory action is indicated.

In addition, DPE represents the Office of Epidemiology and Biostatistics on the Therapeutic Inequivalency Action Coordinating Committee (TIACC). DPE's representative assists in the

investigation and resolution of claims of alleged drug bioinequivalency. In this way, CDER works to prevent injury from drugs that are super-potent or sub-potent because of manufacturing errors.

Pharmacoepidemiology Efforts

CDER's Division of Pharmacovigilance and Epidemiology (DPE) also carries out an epidemiological function in the monitoring of drug safety. This function is performed by a multi-disciplinary professional staff of physicians and Ph.D. epidemiologists, pharmacists and program/project managers. The primary work is directed towards the evaluation and risk assessment of drugs in the postmarketing environment, using the tools of epidemiology.

Epidemiologists integrate the medical/clinical details of the underlying disease being treated with the influence of patient factors, concomitant diseases and medications, as well as the clinical pharmacology of the specific product under study.

DPE's Epidemiology staff work closely with the Post-Marketing Safety Reviewers to provide clinical and epidemiologic case-series reviews of spontaneous adverse event reports submitted to FDA. These data are used in a variety of ways to develop and further refine and investigate signals of clinical importance related to drug safety. As a complement, drug-use data are used frequently to estimate the size and characterize the demographic composition of the population exposed to a given prescription product.

Additionally, epidemiologists are involved in the design and critique of Phase IV protocols for safety studies performed by industry, and in the review of study findings. They also design, execute and help to analyze data from epidemiologic studies performed through the mechanism of the DPE's cooperative agreement program which provides the Center with access to several large record-linked databases.

The reports produced by DES are integral to the ongoing risk assessment and risk management performed by CDER review divisions of a product's risk vs. benefit profile. In addition, DPE epidemiologists are called upon to meet with industry over important safety issues or to present their work before FDA advisory committees.

Contracts/Cooperative Agreements

Externally, the Agency uses a mix of contracts and cooperative agreements (an interactive form of a grant) to address a variety of drug exposure and risk issues. Each of these cooperative agreements and contracts have a distinct purpose that is vital to the surveillance and evaluation of drug safety issues on a national level. The contracts are used to gain access to databases to help obtain answers to questions that the FDA has regarding particular drugs. The Agency defines a specific need, generates a request or a protocol, and the contractor makes a delivery of data or a report.

CDER's Division of Pharmacovigilance and Epidemiology (DPE) has several contracts used for pharmacoepidemiologic and drug safety evaluation. One such contract is a drug marketing database used for describing and estimating use of many drugs. The database also provides various patient demographics.

Cooperative agreements are extensions of the federal grants process that allows federal scientists to work with scientists in academia and the private sector. These agreements create a mechanism for the government to participate in inquiries and research on issues of adverse drug reactions with scientists and databases that would otherwise be beyond the resources of the Agency if they were to be funded as contracts.

DPE is able to work with several grantees who have a variety of data and scientific resources at their disposal and for which each grantee is an expert. For instance, one grantee might have a large elderly population, while another will have strength such as the ability to link mothers and their drug usage during pregnancy to pregnancy outcomes.

Prescription Drug Advertising and Promotional Labeling

Part of CDER's mission is to assure that prescription drug information provided by drug firms is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement, and education program, and by fostering better communications of labeling and promotional information to both health professionals and consumers. This work is accomplished primarily through CDER's Division of Drug Marketing, Advertising and Communications (DDMAC).

- Promotional Materials Review Process- An interactive chart that provides an overview of CDER's process for reviewing and monitoring prescription drug advertising and promotional labeling provided by drug firms..... 50

- DDMAC Home Page- Click here for further information on CDER's Division of Drug Marketing, Advertising and Communications.

Also...

- Advertising/Labeling Definitions..... 56
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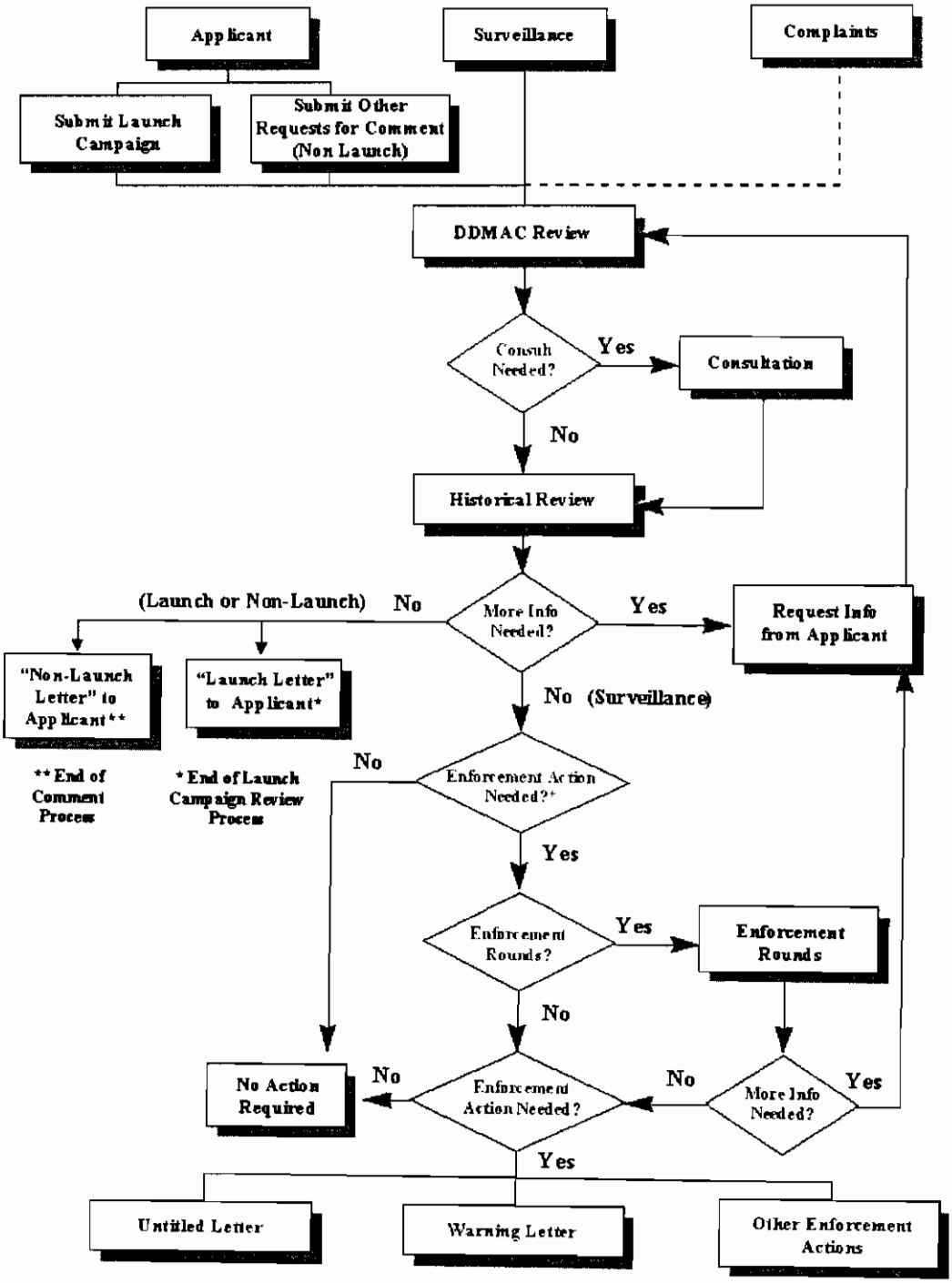
Promotional Material Review Process



Applicant

A company with an approved new drug application (NDA), abbreviated new drug application (ANDA), or abbreviated antibiotic drug application (AADA) that submits one or more promotional pieces.

Submit Launch Campaign

Launch campaigns are introductory promotional campaigns for a new drug or for a new indication or dosage for an already marketed drug. The campaigns usually contain a variety of promotional pieces, such as detail aids, monographs, advertisements, and press kits.

DDMAC advises the pharmaceutical industry on proposed advertising and promotional labeling, as specified in 21 CFR 202.1(j)(4). DDMAC has requested in guidance to industry that launch campaigns be submitted voluntarily to DDMAC for comment before dissemination. Launch campaigns are DDMAC's highest review priority, because these campaigns create the initial and often lasting impression to prescribers regarding the product's safety and efficacy. Reviewers generally respond to applicants within 2 to 3 weeks after the product is cleared for marketing or after the labeling issues have been negotiated.

Submit Other Requests for Comment

Under 21 CFR 10.85, companies may request an advisory opinion on promotional pieces before the pieces are used by the company. DDMAC will provide comments on these pieces as time permits and based on the division's work priorities.

Surveillance

DDMAC monitors prescription drug promotion for compliance with the law. Promotion cannot be false or misleading and must be presented with fair balance. Types of promotion include, but are not limited to, detail aids, sales aids, journal ads, direct-to-consumer ads, product information on the Internet, and radio and TV advertisements.

DDMAC conducts surveillance in a variety of ways:

I. Submissions from drug applicants:

FDA's regulations at 21 CFR 314.81(b)(3)(I) require drug applicants to:

> . . . submit specimens of mailing pieces and any other labeling devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. . . . Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling.

DDMAC reviews these pieces to determine if they meet the requirements of the Act and the regulations.

To obtain Form FDA 2253, write to the following address:

PHS Forms and Publications Distribution Center
12100 Parklawn Drive
Rockville, MD 20857

2. Conferences: DDMAC staff attend medical professional conferences where they observe company exhibition booths and collect promotional materials to review.

DDMAC Review

Launch campaigns, Form FDA-2253 submissions, materials obtained through surveillance activities, and complaints are assigned to the DDMAC reviewer responsible for that drug or product class. Reviewers evaluate whether the materials meet the requirements for advertising or promotional labeling. Complaints follow a slightly different review process.

See Advertising/Labeling Definitions section for an understanding of what constitutes prescription drug advertising and promotional labeling.

Consultation

When necessary, there are a variety of different consults that are obtained within the Center regarding prescription drug advertising and promotional labeling issues:

- Direct-to-Consumer Advertising Consult

  Advertising directed to consumers must meet the same requirements as promotion directed to health professionals. Drug application reviewers may send direct-to-consumer (DTC) advertising pieces to the DDMAC consultant on DTC issues to ensure consistency in applying the regulations to this type of advertising. DTC advertisements are often printed in popular magazines and journals that are read by a broad audience.

- Pharmacoeconomics/Managed Care Consult

  Consults for pharmacoeconomic and managed care issues may be sent to the epidemiologist in DDMAC to determine whether related claims meet the requirements of the regulations. Pharmacoeconomics refers to the measurement of the costs and effects of pharmaceuticals in terms of price, cost-effectiveness and other cost ratios, and quality of life.

- Medical Consult

  DDMAC reviewers work closely with medical review staff when evaluating scientific claims

used in promotional materials and contact the medical staff regarding scientific questions about products.

- Statistical Consult

  DDMAC reviewers may ask CDER statisticians to provide a consult on issues requiring statistical interpretation.

Historical Review

DDMAC reviewers review the files for a product's previous promotional pieces and for competing products in the same therapeutic class.

"Launch Letter" to Applicant

A "launch letter" is a letter in response to an applicant's launch campaign submission. DDMAC reviewers provide the applicant with comments about the proposed launch campaign. Letters are reviewed by and receive the concurrence of appropriate managers.

Enforcement Rounds?

Reviewer decides whether issue needs to be discussed at "enforcement rounds" meeting. This is a weekly DDMAC meeting devoted to discussing regulatory concerns, complaints, enforcement options, and status of actions.

Enforcement Rounds

"Enforcement rounds" is a weekly DDMAC meeting devoted to discussing regulatory concerns, complaints, enforcement options, and status of actions regarding advertising under review in the division.

Untitled Letter

Untitled letters address promotion violations that are less serious than those addressed in warning letters. A reviewer's untitled letter is peer-reviewed and has the concurrence of the branch chief. In such letters, DDMAC usually requests that a company take specific action to bring the company into compliance within a certain amount of time, usually 10 working days. There is no requirement that the agency take enforcement action, although the letters may serve as a basis for additional regulatory action.

Warning Letter

Warning letters are written communications from FDA, in this case DDMAC, to a company notifying the company that DDMAC considers one or more promotional pieces or practices to be

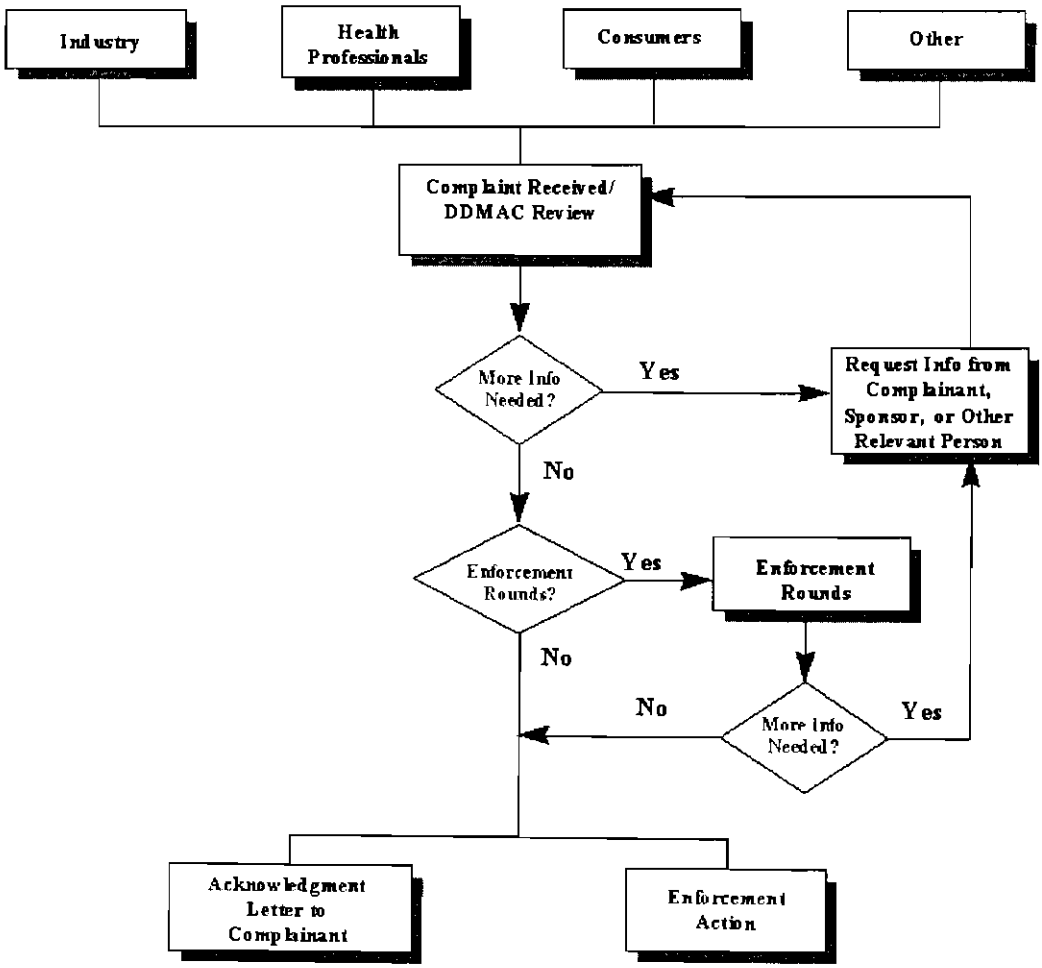
in violation of the law. If the company does not take appropriate and prompt action, as requested in the warning letter, to correct the violation, there may be further enforcement action without further notice.

Warning letters are issued by the DDMAC Division Director and receive concurrence from appropriate officials in the Center for Drug Evaluation and Research. Companies have 15 working days to respond to the warning letter. Warning letters are put on display at the time of issuance in FDA's Freedom of Information office.

Other Enforcement Actions

Other possible enforcement actions include recalls, seizures, injunctions, administrative detention, and criminal prosecution.

Promotional Material Review Process (Complaints)



Advertising/Labeling Definitions

Q. What is prescription drug advertising?

21 CFR 202.1(l)1 states that advertisements subject to Section 502(n) of the Food, Drug, and Cosmetic Act (FD&C Act) include advertisements published in journals, magazines, other periodicals, and newspapers; and broadcast through media such as radio, television, and telephone communications systems. This is not a comprehensive list of advertising media subject to regulation. For example, FDA also regulates advertising conducted by sales representatives, on computer programs, through fax machines, or on electronic bulletin boards.

Q. What must a prescription drug advertisement include?

Under section 502(n) of the FD&C Act, advertisements must include: the established name, the brand name (if any), the formula showing quantitatively each ingredient, and information in brief summary which discusses side effects, contraindications, and effectiveness. The brief summary is further discussed in 21 CFR 202.1(e)(1).

Q. Are there exceptions to the advertising regulations?

Yes, there are a few exceptions but only to the requirement to provide a true statement of information in brief summary as required under 21 CFR 202.1(e)(1). 21 CFR 202.1(e)(2) describes which ads are exempt:

1. Reminder advertisements - advertisements which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the product, or any other representation. Reminder ads contain the proprietary name of the drug and the established name of each active ingredient. They may also contain additional limited information, such as the name of the company, price, or dosage form.

The exception does not apply to products with black box warnings in their approved product labeling.

2. Advertisements of Bulk-sale drugs - promote sale of the drug in bulk packages to be processed, manufactured, labeled, or repackaged and that contain no claims for the therapeutic safety or effectiveness of the drug.

3. Advertisements of prescription-compounding drugs - promote sale of a drug for use as a prescription chemical or other compound for use by registered pharmacists.

Q. What is labeling?

Section 201(m) of the FD&C Act states labeling ". . . means all labels and other written, printed, or graphic matter . . . accompanying such article."

The regulations provide examples of labeling under 21 CFR 202.1(l)(2):

"Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the FD&C Act."

Q. What must labeling include?

Labeling must include the established name, proprietary name (if any), adequate directions for use, and adequate warnings. The agency considers the approved product labeling, sometimes called the full prescribing information, to be adequate directions for use and adequate warning.

Q. Are there exceptions to the requirements for labeling?

Yes. Reminder labeling is exempt from the requirements for adequate directions for use and adequate warnings. Reminder labeling, as defined in 21 CFR 201.100(f), is exempted. Reminder labeling calls attention to the name of the drug product but does not include indications or dosage recommendations for use. Reminder labeling may contain only the proprietary name of the drug, the established name of each active ingredient, and optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, and other limited information.

The exemption does not apply to products with black box warnings in their approved product labeling.

Labeling Research Activities

CDER's Division of Drug Marketing, Advertising and Communications (DDMAC) conducts research to improve the design and format of labeling for prescription and over-the-counter drugs.

- In cooperation with CDER's Office of the Center Director, DDMAC is examining how to improve communication of prescribing information through the revision of professional labeling format.

- DDMAC is working with CDER's Division of Over-The-Counter (OTC) Drug Products to develop and test formats for OTC labels (the information that is on the box or container).

Patient Information and Education Activities

CDER's Division of Drug Marketing, Advertising and Communications conducts and monitors research on factors that may influence or improve drug use by consumers, patients, and health care professionals.

- Objective 12.8 of Healthy People 2000: This objective reads: "Increase to at least 75% the proportion of people who receive useful information verbally and in writing for new prescriptions from prescribers or dispensers." Two approaches undertaken by FDA to influence private sector initiatives are: (1) the development of performance goals for the quantity as well as the quality of distributed information and (2) research and development activities to better understand how to communicate prescription drug information to patients.

- Medication Guides: A proposed rule for Medication Guide requirements was published on August 24, 1995. The proposed rule was intended to increase the dissemination of useful written prescription drug information to patients who receive prescription drugs on an outpatient basis. FDA believes that such information must be widely distributed and be of sufficient quality to promote the proper use of prescription drugs. The agency proposed goals (performance standards) that would define acceptable levels of information distribution and quality. To meet the performance standards for distribution of patient information, the agency proposed that by the year 2000, at least 75% of people receiving new prescriptions receive useful written information. This goal was adapted from the Public Health Service's "Healthy People 2000" report. In addition, the agency proposed that by the year 2000, at least 95% of the people who receive new prescription drugs receive useful written information.

  A public meeting was held in February 1996 to discuss standards for Medication Guides. In August 1996, Congress passed a law requiring that the private sector be given the opportunity to develop a plan, acceptable to the Department of Health and Human Services (DHHS), to reach the goals specified in the proposed Medication Guide rule. On December 13, 1996, the private sector steering committee submitted its plan to reach these goals. The Secretary of DHHS accepted the plan on January 13, 1997. FDA will continue to assess progress toward the goals and to assist the private sector to achieve them in the specified time frames.

- Prescription Drug Counseling Surveys: Trends in providing prescription drug information have been followed through periodic surveys of people who recently obtained a new prescription at a retail pharmacy. Nationwide surveys have been undertaken in 1982, 1984, 1992, and 1994. Data from the surveys have been used to support proposed regulations and private sector initiatives in improving the quality and quantity of drug information. Data collection from the 1996 survey has recently been completed and analysis is under way.

- Women's Health: A study is being undertaken to investigate gender differences in consumer understanding of and response to the presentation of risk and benefit information about medications. A questionnaire to assess men's and women's understanding of risk and benefit

communications was recently approved by the Office of Management and Budget (OMB). Research funds are being sought from the Office of Women's Health. By examining gender differences in processing benefit and risk information, the goal is to develop ways of presenting labeling for patients that are useful and meaningful to all patients.

- Over-the-Counter (OTC) Labeling: Studies to evaluate newly proposed formats and labeling language for OTC drugs are being designed. Focus group testing is currently under way.

Policy Development and Guidance to Industry

CDER's Division of Drug Marketing, Advertising and Communications (DDMAC) develops guidances to the industry on prescription drug advertising and promotional labeling issues. In addition, the division holds meetings with the regulated industry and other involved parties to discuss emerging issues, such as broadcast, direct-to-consumer, and Internet advertising, and use of cost effectiveness and quality of life claims in promotion. DDMAC communicates its interpretations of the regulations to the industry through guidance documents that are published in the Federal Register and made available to the public on the World Wide Web or from the Drug Information Branch, Division of Communications Management, HFD-210, CDER.

For guidance specific to a drug or therapeutic class, DDMAC works with the appropriate new drug review division to ensure that division's concerns are adequately addressed in the guidance.

Some of the Policies and Guidances Currently Under Development

- ***Revision of Previous Guidances***- DDMAC is revising all guidances it has issued since 1970 to determine if they are obsolete or need revision. A series of Federal Register notices will explain the changes and give the public an opportunity to comment.

- ***Direct-to-consumer advertising and promotion***- With other FDA offices, DDMAC is examining whether the current advertising and labeling regulations should continue to apply to promotion directed to consumers, or whether there should be changes made in the requirements for this type of promotion.

- ***Promotion on the Internet***- As part of an FDA working group, DDMAC is developing an agency-wide policy to address how advertising and promotion of FDA-regulated products will be regulated on the Internet.

- ***Promotion to managed care organizations***- DDMAC is developing a policy regarding pharmaceutical marketing, pharmacoeconomic claims, and information exchange in managed care environments.

- ***Quality of Life Claims***- DDMAC is developing a policy regarding the claims made in labeling and advertising about the impact of pharmaceuticals on the quality of life.

Pharmaceutical Industry Surveillance

Government oversight of the pharmaceutical industry is usually classified into preapproval and post-approval categories. Most of the therapeutically significant compounds marketed today are the subject of new drug applications (NDAs) and abbreviated new drug applications (ANDAs). Preapproval activities, based on these detailed applications, are used to assure the drug is safe and effective before marketing. The Center for Drug Evaluation and Research (CDER) is the FDA organization responsible for drug evaluation and approval. Before approval, the FDA may inspect and audit the development facilities, planned production facilities, clinical trials, institutional review boards, and laboratory facilities in which the drug was tested in animals.

After the drug is approved and marketed, the FDA uses different mechanisms for assuring that firms adhere to the terms and conditions of approval described in the application and that the drug is manufactured in a consistent and controlled manner. This is done by periodic unannounced inspections of drug production and control facilities by FDA's field investigators and analysts. These professionals are organized under FDA's Office of Regulatory Affairs (ORA), which has twenty-one district offices and many more resident posts throughout the country.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides legal authority for inspections and access to factories, vehicles, equipment, records, processes, and controls necessary to determine that drugs are being produced in conformance with regulations that have the force of law. These regulations, Current Good Manufacturing Practice for Finished Pharmaceuticals, are contained in Part 211 of Title 21 of the U.S. Code of Federal Regulations. These regulations contain requirements for: Organization and Personnel; Buildings and Facilities; Equipment; Components, Containers, and Closures; Production and Process Control; Packaging and Labeling; Distribution; Laboratory; and Reports and Records.

The regulations are general enough to be applied to a wide variety of dosage form drugs from topical ointments and creams to sterile injectables and ophthalmics. Yet, they are specific enough to require: testing of every batch for conformance with specifications before release, manufacture according to a specific master formula and process, validation of all manufacturing and control processes, investigation of complaints and failures, annual evaluation of products, testing program to assure stability of product throughout its labeled life, and testing of components and ingredients.

FDA investigators often use additional information from a variety of market surveillance systems to assist them in identifying a manufacturing or control problem. Consumer complaints, MedWatch submissions, NDA Field Alerts, Drug Quality Reporting System, and Adverse Drug Experience Reports are some of the systems used to identify drug problems by FDA's epidemiological units. FDA investigators also have access to a large variety of state-of-the-art analytical facilities throughout the country. These laboratories confirm suspected chemical, physical, and microbiological problems with pharmaceuticals; verify and develop analytical methods; and conduct research.

This system of regulation has grown with the pharmaceutical industry through many crises and challenges. The FDA welcomes dialogue with other regulatory bodies, industry organizations, Congress, and the public to improve the efficiency of its regulatory and administrative processes.

For more information, contact the Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) at (301)594-0093, or contact FDA's Office of the Commissioner, Office of Regulatory Affairs at (301)443-6230. You can also visit DMPQ's CGMP Web Page or see the Office of Compliance FY 1996 Annual Report.

Subject-Related CDER Guidances of Interest

- General Principles of Process Validation
- Manufacture, Processing or Holding of Active Pharmaceutical Ingredients
- Drug Master Files

Other Subject-Related Documents of Interest

- Sections 505, 501(a)(2)(B), and 704 of the Federal Food, Drug, and Cosmetic Act as Amended
- 21 CFR Part 211- Current Good Manufacturing Practice for Finished Pharmaceuticals
- CDER Manual of Policies and Procedures 4732.1- The Establishment Evaluation Process (draft)
- Compliance Program Guidance Manual 7346.832, 7346.843, 7356.002, 7356.020

Medication Errors

Medication errors cause at least one death every day and injure approximately 1.3 million people annually in the United States. Medication mishaps can occur anywhere in the distribution system:

- prescribing,
- repackaging,
- dispensing,
- administering, or
- monitoring.

Common causes of such errors include:

- poor communication,
- ambiguities in product names, directions for use, medical abbreviations or writing,
- poor procedures or techniques, or
- patient misuse because of poor understanding of the directions for use of the product.

In addition, job stress, lack of product knowledge or training, or similar labeling or packaging of a product may be the cause of, or contribute to, an actual or potential error.

CDER began receiving reports of medication errors in January 1992, when the U.S. Pharmacopeia began forwarding reports to the FDA. To evaluate and recommend appropriate action on these reports, the Medication Errors Subcommittee was formed in June 1992. In November 1993, the Agency began evaluating and coding MedWatch reports for medication errors and publicly stated that physicians and other health care professionals could report medication errors directly to the FDA through the MedWatch program.

CDER responsibilities are not completed when the safety and effectiveness of a drug product are determined. The Center also has the responsibility for helping to ensure the safe use of the drugs it approves by identifying and avoiding proprietary names that contribute to problems in the prescribing, dispensing, or administration of the product. Because early identification of a potential confusing proprietary name is crucial, CDER reviews these proposed names, prior to approval of a new drug application, by means of the Labeling and Nomenclature Committee.

CDER's approach to medication errors is as follows:

- Prevent medication errors prior to a drug's approval;
- After approval, evaluate, monitor, and take appropriate action on reports of medication errors;
- Educate and provide feedback to health professionals; and
- Share information with outside organizations involved in preventing medication errors.

For more information, see:

- Federal Food, Drug and Cosmetic Act, as Amended Section 502 (e)
- Code of Federal Regulations 21 CFR 201.10 (c); 201.56(b); and 299.4
- American Society of Health System Pharmacists (ASHP) guidelines on the prevention of medication errors, 1993

Drug Shortages

It is FDA's policy to attempt to prevent or alleviate shortages of medically necessary products. Patient "inconvenience" alone is an insufficient basis to classify a product as a medical necessity. However, a drug shortage situation can result from or may involve:

- changes in production, marketing decisions, and changing or increased use patterns for old drug products, and other factors;
- production changes leading to a drug shortage can result from voluntary recalls or FDA regulatory activities;
- shortage of raw materials (foreign as well as domestic), unpredicted or unanticipated disease outbreaks as well as shifts in product demand;
- single source products or circumstances where one manufacturer has a majority of market share;
- an actual or a potential shortage of a drug product; and
- a product is considered to be medically necessary or a medical necessity, if it is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or alternative drug that is determined by medical staff to be an adequate substitute.

The Center has established procedures for the evaluation of drug shortage situations in order that appropriate measures may be promptly activated. The purpose of the procedure is to develop the capability to evaluate potential drug shortage problems, assess the potential public health impact, and propose a plan to resolve the issue.

Reporting Drug Shortages

External reports on drug shortages are received in CDER through a variety of means. One such means is the Drug Shortage System which is maintained by the Center's Drug Quality Reporting System (DQRS). DQRS is the preferred entry point for consumer reports of drug shortages. Other sources of drug shortage information include FDA's Office of Health Affairs, which is a focal point for drug shortage reports from health professionals.

When drug shortage reports are received, the involved manufacturer(s), supplier(s), FDA's field organization, and appropriate Center staff are contacted to determine whether the shortage is caused by production or distribution problems. Most of the complaints received are simple distribution problems that are easily resolved. FDA personnel have been instrumental in identifying and meeting specific shortages of significant tuberculosis drugs, critical antibiotics, antihypertensives, as well as insulin products.

For more information on the Drug Shortage System, contact the Division of Prescription Drug Compliance and Surveillance, Office of Compliance at 594-0101 or see the Office of Compliance FY 1995 Annual Report.

Therapeutic Inequivalence Reporting

In the past 10 years, FDA's Center for Drug Evaluation and Research has received more and more reports of drug products that fail to work in patients because the product simply has no effect or is toxic. These problems are usually attributed to switching brands of drugs.

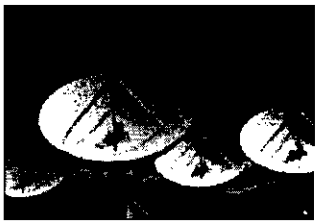
As a result, on Sept. 14, 1988, FDA created in CDER the Therapeutic Inequivalence Action Coordinating Committee (TlACC) to identify and evaluate reports of therapeutic failures and toxicity that could indicate that one product is not equivalent to another similar product. The committee also provides a mechanism for timely follow-up on reports of therapeutic inequivalence and, when, appropriate, conducts a full-scale investigation of these issues.

Once an inequivalent product is identified, TIACC can take a number of actions. These include:

- Removing inequivalent products from the market;
- Evaluating and changing the therapeutic equivalence rating of a product;
- Recommending that a grandfathered product submit a new drug application and require approved generics;
- Testing and evaluating the relationship of dissolution to bioequivalence;
- Recommending appropriate dissolution specifications for narrow therapeutic drugs; and
- Evaluating the toxicitiy profile of injectables and mandate appropriate controls.

For more information, see Federal Register, Sept. 14, 1988, No. 88N-0254.

Communicating with CDER



One of CDER's primary goals is to work collaboratively and cooperatively with industry, academia, and others to improve the drug development and review process. CDER also strives to provide consumers and health care providers with drug information that is vital to improving the public health. The topics listed below provide an overview of the various means of communicating with CDER.

Consumer/Industry Inquiries

The Food and Drug Administration's Center for Drug Evaluation and Research is dedicated to ensuring that all persons involved in, or who depend upon, drug regulation excellence have the information needed to develop, review, market, dispense, prescribe or use drugs safely and effectively.

To enhance the communications aspect of this process, the Center created the Office of Training and Communications' Division of Communications Management (DCM). This division enhances information exchange, strategic communications planning, and the development of communications products and initiatives.

DCM works to ensure that pharmaceutical industry representatives, health care professionals, government officials, and consumers have easy and open access to information, and are educated about the drug regulation process and the benefits and risks of drugs.

Any of these individuals or groups may request information on specific drugs, guidance documents, publications, or general information such as a description of the drug approval process.

There are a number of ways consumers and industry representatives can communicate with or get reliable, current, and up-to-date information from the Center.

- The newest, and easiest, method for getting information is the Center's World Wide Web home page at http://www.fda.gov/cder .
- Another easy method is the Center's Fax-on-Demand system which contains literally hundreds of documents for consumers, industry, Federal, state, and local agencies, and foreign government representatives. The number is 1-800-342-2722.
- For more specific or complex drug inquiries, telephone the Drug Information Branch at (301) 827-4573 or click here to send them an electronic mail message at dib@cder.fda.gov.
- For specific inquiries from industry, telephone CDER's Compendia Operations at (301) 594-0104.

Other sources of information include:

- the FDA Office of Public Affairs, at (301) 443-1130.

In addition, consumers and industry representatives can contact:

- CDER Ombudsman, Jim Morrison, (301) 594-5443;
- FDA Freedom of Information Staff, (301) 827-6567;
- FDA MedWatch Office at 1-800-FDA-1088;
- AIDS Clinical Trials Information Service, 1-800-TRIALS-A or on the World Wide Web at http://www.actis.org. [Notice: This link will take you outside the CDER web site].

Regulatory Correspondence

There are a number of ways that regulated industry can formally or informally communicate with or get information from the Center.

The Center is making available large amounts of information to regulated industry on CDER's World Wide Web home page at http://www.fda.gov/cder.

For general drug information, contact the Center's Drug Information Branch by mail at CDER, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, MD 20857; telephone (301) 827-4573; electronic mail dib@cder.fda.gov.

Specific comments or suggestions on CDER operations may be sent to CDER's Ombudsman, James C. Morrison, at CDER Ombudsman (HFD-1), 5600 Fishers Lane, Rockville, MD 20857; telephone (301) 594-5443; FAX (301) 594-5298 or 594-6197.

Additional expert sources may be found in CDER's ***Quick Index to General Subjects of Interest Related to Drug Regulation***.

Videoconferencing

The Food and Drug Administration's Center for Drug Evaluation and Research has installed state-of-the-art videoconferencing technology for communicating with employees inside the organization as well as with industry representatives, consumers, healthcare professionals, academia, and other government agencies.

CDER's videoconferencing enhances face-to-face meetings by allowing participants the opportunity to listen, watch and participate "live" in a normal two-way conversation.

Videoconferencing can be used for such diverse purposes as:

- delivering a speech to an overseas audience from CDER facilities;
- "attending" a committee meeting being held in another city;
- interviewing prospective new employees;
- "attending" a training session being held in another city;
- holding a product review meeting with a division located in another CDER building.

CDER currently has videoconferencing capabilities in the Parklawn building, Woodmont Office Complex II, and Corporate Boulevard building.

For more information on the Center's videoconferencing capabilities or to schedule an event, telephone CDER's Office of Training and Communications at (301) 827-1243.

CDER Ombudsman

The Center for Drug Evaluation and Research's Ombudsman is responsible for receiving complaints, investigating and acting on them, mediating disputes, and attending to problems involving interpersonal working relationships. In addition, the ombudsman is responsible for getting feedback from inside and outside the Center about the effectiveness of programs and about problems that impede the performance of CDER's mission or conflict with its values/operating principles. The ombudsman also advises the Center Director on ways to correct such problems.

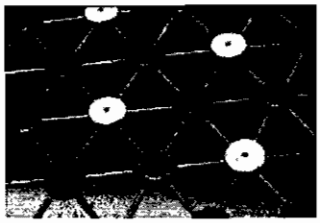
For more information, visit the CDER Ombudsman home page.

To speak with the CDER Ombudsman, James C. Morrison, phone (301) 594-5443 or fax (301) 594-5298 or (301) 594-6197.

In addition, you can send correspondence to him at:

CDER Ombudsman (HFD-1)
5600 Fishers Lane
Rockville, MD 20857

Other Activities



There are many other activities that CDER is involved in that contribute to its mission of assuring that safe and effective drugs are available to the American people. The topics listed below highlight some of these major activities.

Orphan Drugs

The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The Orphan Drug Act was signed into law on January 4, 1983. Since the Orphan Drug Act passed, over 100 orphan drugs and biological products have been brought to market.

The intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat rare diseases. This mission is accomplished through several mechanisms:

- Sponsors are granted seven years of marketing exclusivity after approval of its orphan drug product.
- Sponsors also are granted tax incentives for clinical research they have undertaken.
- FDA's Office of Orphan Products Development coordinates research study design assistance for sponsors of drugs for rare diseases [Notice: This link will take you outside the CDER web site].
- The Office of Orphan Products Development also encourages sponsors to conduct open protocols, allowing patients to be added to ongoing studies.
- Grant funding is available to defray costs of qualified clinical testing expenses incurred in connection with the development of orphan products.

Drug Registration and Listing System

FDA attempted a comprehensive drug inventory for drug listings by establishing two voluntary programs. However, these two *voluntary* programs were unsuccessful. In order to make these efforts mandatory, FDA instituted the Drug Listing Act of 1972, this regulatory policy is in the ***21 Code of Federal Regulations (CFR) Part 207***. The ***21 CFR Part 207*** addresses definitions, drug registration requirements, and drug listing requirements by FDA. This Act amended Section 510 of the Federal Food, Drug, and Cosmetic Act and defines the applicable following terms:

- The term *Firm* refers to a company engaged in the manufacture, preparation, propagation, compounding, or processing of a drug product.
- The term *Drug Products* refers to human drugs, veterinary drugs, and medicated animal feed premixes which includes biological products, but does not include blood and blood components.
- The term *Manufacturing and Processing* refers to repackaging or otherwise changing the container, wrapper, or labeling of any drug product package in the distribution process from the original "maker" to the ultimate consumer.

Registration Requirements

A firm must register all drug products (Domestic Manufacturers, Domestic Repackers, Domestic Labelers, and submissions for New Human Drug Application, New Animal Drug Application, Medicated Feed Application, Antibiotic Drug Application, and Establishment License Application to Manufacture Biological Products) whether or not they enter interstate commerce. All domestic distributors and foreign firms importing drug products into the United States must obtain a labeler code and list all of their products.

Listing Requirements

All firms, unless exempted by the Act, are requested to list their commercially marketed drug products with FDA within 5 days after the beginning of operation. They are required to list/update their drug products listing twice a year (June and December). The initial listing and updates of a product is done on a form FDA 2657. Manufactures are allowed to list the products for distributors on form FDA 2658. In order to assist the firms with the mandatory update in June, the Product Information Management Branch mails a Compliance Verification Report (CVR) to the firms. The CVR goes to all firms which have at least one prescription product listed with FDA. The firm is required to update the CVR and mail it back within 30 days.

Registration Exemptions

Pharmacies, hospitals, and clinics that dispense drug products at retail; licensed physicians who use drug products solely for purposes related to their professional practice; and/or persons using drug products solely for their professional needs and are not for sale are exempt from registration. [See ***21 CFR 207***]

Registration Process

Firms can register by obtaining a Registration of Drug Establishment Form, FDA 2656 within 5 days after the beginning of operation or submission of an application. Firms are required to re-register annually by returning an Annual Registration of Drug Establishment Form, FDA 2656E, within 30 days after receiving it from the Product Information Management Branch.

For More Information:

For further information, or to obtain copies of Forms FDA 2656, FDA 2656E, FDA 2657, FDA 2658 or the Drug Registration and Listing Instruction Booklet (May 1996), contact CDER's Product Information Management Branch, Division of Database Management, HFD-58 at (301)594-1086.

Environmental Assessments

Under the National Environmental Policy Act of 1969 (NEPA), all Federal agencies are required to assess the environmental impact of their actions and to ensure that the interested and affected public is informed of the environmental analyses. CDER's ***Guidance for Industry for the Submission of an Environmental Assessment*** provides detailed information on a variety of topics related to preparing and filing environmental assessments (EAs).

In CDER, adherence to NEPA is demonstrated by the EA portion of the drug application. This section focuses on the environmental implications of consumer use and disposal from use of the candidate drug. However, because approval of many drugs are unlikely to have significant environmental effects, CDER has provisions for submission of abbreviated EAs rather than full EAs under certain circumstances or has categorically excluded certain classes of actions. FDA has reevaluated its NEPA regulations found in ***21 CFR Part 25*** and has proposed to improve its efficiency in the implementation of NEPA and reduce the number of EAs by increasing the number of applicable categorical exclusions. The notice of proposed rule making was posted in the Federal Register on April 3, 1996.

Women's Health Issues

CDER strongly supports activities on women's health issues through the Women's Health Subcommittee of the CDER Medical Policy Coordinating Committee.

Primary among these projects is the FDA Pregnancy Labeling Task Force which CDER co-chairs and manages. This task force was organized to review pregnancy labeling and to explore how the category information could be presented to clinicians, reviewers and other interested parties in the most effective manner in order to provide the greatest possible usefulness to the public. The long term goal is to determine how animal toxicology information contributes to clinically meaningful information. A major task of this group will be the reassessment of Category "C". Because of the traditional approach the FDA has taken, most drugs have been placed in this category. This has resulted in the erroneous appearance that there are few drugs which can be safely given to women of childbearing potential.

Other women's health projects in which CDER is participating are the Pregnancy Registry Working Group, the Pregnancy Drug Use Survey, rewriting of the Institutional Review Board regulations to foster studies in which women of child-bearing potential are included, and gender-related bioequivalence issues.

The FDA Consumer magazine, an official publication of the FDA, featured the Office of Women's Health in an article in the October 1996 issue entitled, "***InsideFDA: Office of Women's Health***." The FDA Office of Women's Health itself has established and maintains a Web site containing information on a broad range of issues related to women's health. [Notice: These two links will take you outside the CDER web site]. In addition, the page is linked to a variety of other sources inside and outside of FDA which provide information on topics of related interest.

Pregnancy "Category C" Labeling

An FDA Pregnancy Labeling Task Force was organized to review drug labeling information on pregnancy and fetal risks and to explore how the information could be presented to clinicians, reviewers and other interested parties in the most effective manner, in order to provide the greatest possible usefulness to the public. The long term goal is to determine how animal toxicology information contributes to clinically meaningful information. A major task of this group is the reassessment of category "C." Specific requirements on content and format of labeling for human prescription drugs states the following:

> Pregnancy Category C: If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (Name of drug) has been shown to be

teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

CDER Pediatric Initiatives

CDER is actively involved in initiatives related to the improvement of children's health. This is accomplished primarily through CDER's Pediatric Subcommittee of the Medical Policy Coordinating Committee. The Pediatric Subcommittee has been charged with providing expert advice and promoting the development of medicines in the pediatric population. Following is a list of initiatives of the Pediatric Subcommittee.

Pediatric Use Regulations

• On December 12, 1994, FDA published a final rule revising the current pediatric use subsection of the professional labeling requirements for prescription drugs to broaden the basis on which information about use of a drug in the pediatric population may be included. The new regulation allows evidence of effectiveness in adults to be used as a basis for concluding that a drug is effective in the pediatric population if the course of the disease and effects of the drug are sufficiently similar in adults and the pediatric population to permit such extrapolation. Additional information supporting the pediatric use (e.g., pharmacokinetics data, safety data, pharmacodynamics data) should also usually be submitted to determine the appropriate pediatric dose.

• On August 15, 1997, FDA published a proposed rule that would require manufacturers to assess the safety and effectiveness of new drugs and biologics in pediatric patients. The 1994 regulation simplified the required pediatric data in order to encourage drug manufacturers to submit these data voluntarily for review. However, many new drugs are still being approved without information on how they should be used in children. In addition to new drugs, the proposed rule would also apply to many drugs already approved and being used. For drugs that are already marketed, this regulation would codify FDA's authority to require, in compelling circumstances, that manufacturers conduct studies to support pediatric-use labeling for the approved indications.

Guidance for Industry- In March 1996, FDA published the guidance for industry *The Content and Format for Pediatric Use Supplements* . This guidance provides information on the content and format of pediatric use supplements submitted in response to the December 1994 final rule.

Pediatric Drug Use Survey- CDER has obtained information on those approved drugs most frequently used in the outpatient pediatric population without adequate pediatric labeling and has sent letters to those commercial sponsors identified in this survey requesting that the sponsor contact the agency regarding their intention to submit a pediatric use labeling supplement.

Communication with Industry- CDER has begun focusing on the pediatric population throughout the clinical drug development. CDER has identified key opportunities for discussing with commercial sponsors the plan for pediatric development of a drug:

- Pre-IND and pre-IND submission meetings
- Initial IND submission
- IND annual report
- End of phase 2 meeting
- Presentation of IND to an FDA drug advisory committee
- Pre-NDA meeting
- NDA submission and FDA's 45-day filing meeting
- Presentation of NDA to an FDA drug advisory committee

Pediatric Page- CDER and the Center for Biologics Evaluation and Research (CBER) have revised the pediatric page and will extend its use to all NDAs/PLAs/PMAs/efficacy supplements for all action letters. The pediatric page summarizes the state of pediatric studies at the time an action is taken on an application. It is currently used only for approvals of new molecular entities. CDER is currently in the process of implementing a tracking system for the pediatric page.

Revised Pediatric Guidelines- CDER will be revising the 1977 guidance *General Consideration for the Clinical Evaluation of Drugs in Infants and Children* to reflect changes in drug development by focusing on earlier consideration of the pediatric population during the clinical evaluation of pharmaceuticals and extrapolation of adult data.

Pediatric Pharmacology Research Units (PPRU)- CDER collaborates with PPRU's regarding the development and conduct of clinical and pharmacokinetic studies of drugs in the pediatric population. CDER has proposed clinical trials on specific drugs or pediatric formulations without commercial sponsorship.

Pharmacokinetic Guidance- CDER and CBER have drafted a guidance for industry, *General Considerations for Pediatric Pharmacokinetic Studies*. The document provides guidance to those researchers interested in conducting pharmacokinetic studies in the pediatric population. The document is currently under review within the Center.

Pediatric Rapid Response Team- A team has been established to assist reviewers on pediatric issues on a day-to-day basis. The team consists of 4-5 rotating members from the Pediatric Subcommittee. Rotating members volunteer for 3 months at a time. The team will provide expert advice to reviewers on issues related to pediatric drug development. The team will strive to answer questions in a timely fashion (1-2 week turnaround time).

NDA Periodic Pediatric Use Report- CDER is in the process of modifying the regulations for the postmarketing periodic reports of adverse events to include information regarding the age of the patient and the diagnosis for which the drug was prescribed, with special emphasis on the pediatric population (21 CFR 314.80) as well as the NDA annual reports. This proposal will be harmonized with the International Conference on Harmonisation efficacy guidance *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* to prevent any overlap or duplication of requirements.

"International Conference on Harmonisation"

As a Center within FDA, CDER, along with the Center for Biologics Evaluation and Research (CBER), is an active participant in the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH).

This unique undertaking is a cooperative effort between the drug regulatory authorities and the innovator pharmaceutical company professional organizations in the European Union, Japan and the United States to reduce the need to duplicate the testing conducted during the research and development of new medicines.

Through harmonization of the technical guidelines and requirements under which drugs for human use are approved within the participating nations, ICH members seek more economical use of human, animal and material resources and the elimination of delay in availability of new drugs, while maintaining the quality, safety and effectiveness of regulated medicines.

Information on this international initiative is available through the official ICH Home Page on the World Wide Web [Notice: This link will take you outside the CDER web site]. The ICH Secretariat maintains this web site and is responsible for the accuracy of the information it contains. In addition, CDER's Office of Training and Communications, through its Drug Information Branch, makes available a current list of ICH guidance documents. If you access this page, scroll down to the section entitled ***International Conference on Harmonisation***. Also, information regarding many of FDA's international activities will soon be available via the FDA web site.

People at CDER

The Center for Drug Evaluation and Research is a dedicated community of scientists, professionals and support staff who work to assure that safe and effective drugs are available to the American people. Listed below are links to information (in PDF format) on how CDER is organized as well as to key points of contact within the Center.

- Office of the Center Director
- Office of Review Management
- Office of Pharmaceutical Science

Also..

- CDER Organization Chart
- Quick Index to General Subjects of Interest Related to Drug Regulation- Contacts for specific IND/NDA topics.
- CDER Key Officials List
- CDER Employee Directory (Alphabetical)
- DHHS Employee Directory (maintained by DHHS)
- CDER Fax Directory

EXHIBIT 13

Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2005
Clinical Medical

Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training, and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
March 2005
Clinical Medical

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1] Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).[2] Specifically, this document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

[1] This guidance has been prepared by the PDUFA III Pharmacovigilance Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For ease of reference, this guidance uses the term *product* or *drug* to refer to all products (excluding blood and blood components) regulated by CDER and CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

A. PDUFA III's Risk Management Guidance Goal

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9 – 11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

B. Overview of the Risk Management Guidances

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

  Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (see e.g., FDA requirements for professional labeling, and adverse

event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

  During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.[3]

- To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as appropriate.

  The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

- When planning risk assessment and risk minimization activities, sponsors should consider input from health care participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and third party payers).

- There are points of overlap among the three guidances.

  We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

III. THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

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[3] See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii), and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see http://www.hhs.gov/ocr/hipaa.

This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

A. Good Reporting Practice

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events,[4] and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

[4] Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on *Postmarketing Reporting of Adverse Experiences*, (3) FDA guidance for industry on *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)*, (4) FDA guidance for industry on *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

B. Characteristics of a Good Case Report

Good case reports include the following elements:

1. Description of the adverse events or disease experience, including time to onset of signs or symptoms;

2. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;

3. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;

4. Documentation of the diagnosis of the events, including methods used to make the diagnosis;

5. Clinical course of the event and patient outcomes (e.g., hospitalization or death);[5]

6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;

7. Information about response to dechallenge and rechallenge; and

8. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following, when such information is available:

1. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);

2. Sequence of events leading up to the error;

3. Work environment in which the error occurred; and

4. Types of personnel involved with the error, type(s) of error, and contributing factors.

[5] Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy.[6] Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

C. Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)). When available, FDA recommends that standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.[7] In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);

2. Absence of symptoms related to the event prior to exposure;

3. Evidence of positive dechallenge or positive rechallenge;

4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;

5. Consistency of the event with the known effects of other products in the class;

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[6] See http://www.nccmerp.org for the definition of a medication error and taxonomy of medication errors.

[7] See, for example, Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and

7. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories *probable, possible,* or *unlikely* have been used previously.[8] If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event.[9] FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the *medication use systems* (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors.

D. Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. The clinical and laboratory manifestations and course of the event;

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[8] See World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Product,* for additional categorizations of causality.

[9] See Cohen MR (ed), 1999, *Medication Errors*, American Pharmaceutical Association, Washington DC; Cousins DD (ed), 1998, *Medication Use: A Systems Approach to Reducing Errors*, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

2. Demographic characteristics of patients with events (e.g., age, gender, race);

3. Exposure duration;

4. Time from initiation of product exposure to the adverse event;

5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;

6. Use of concomitant medications;

7. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;

8. The route of administration (e.g., oral vs. parenteral);

9. Lot numbers, if available, for products used in patients with events; and

10. Changes in event reporting rate over calendar time or product life cycle.

E. Use of Data Mining to Identify Product-Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called *data mining*, can provide additional information about the existence of an excess of adverse events reported for a product. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with (2) the fraction of reports for the same particular event for all drugs (i.e.,"the expected reporting fraction").[10] This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product-event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product-event combination with a score exceeding the specified threshold. When

[10] Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

applying data mining to large databases (such as AERS), it is not unusual for a product to have several product-event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm[11,12], the Proportional Reporting Ratio (PRR) method[13,14]and the Neural Network approach.[15] Except when the observed number of cases with the drug event combination is small (e.g., less than 20) or the expected number of cases with the drug event combination is < 1, the MGPS and PRR methods will generally identify similar drug event combinations for further investigation.[16]

Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products. FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g., some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other co-morbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, under-reporting, or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g., statistical algorithm, and the drugs, events and

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[11] DuMouchel W and Pregibon D, 2001, Empirical Bayes screening for multi-item associations, *Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining*.

[12] Szarfman A, Machado SG, and O'Neill RT, 2002, Use of sereening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety* 25(6): 381-92.

[13] Evans SJW, Waller P, and Davis S, 1998, Proportional reporting ratios: the uses of epidemiological methods for signal generation [abstract], *Pharmacoepidemiology and Drug Safety* 7:S102.

[14] Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

[15] Bate A et al., 1998, A Bayesian neural network method for adverse drug reaction signal generation, *European Journal of Clinical Pharmacology* 54:315-21.

[16] This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, M.D., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

stratifications selected for the analyses) or an appropriate reference, and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug-event combination of interest (e.g., results from preclinical, clinical, pharmacoepidemiologic, or other available studies).

F. Safety Signals That May Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. New unlabeled adverse events, especially if serious;
2. An apparent increase in the severity of a labeled event;
3. Occurrence of serious events thought to be extremely rare in the general population;
4. New product-product, product-device, product-food, or product-dietary supplement interactions;
5. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);
6. Confusion about a product's name, labeling, packaging, or use;
7. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);
8. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal);[17] and
9. Other concerns identified by the sponsor or FDA.

G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment.

[17] For a detailed discussion of risk minimization action plan evaluation, please consult the *RiskMAP Guidance.*

In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because:

1. Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;

2. It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low;[18] and

3. A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator.[19,20] FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from: (1) national health statistics, (2) published medical literature, or (3) ad hoc studies, particularly of

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[18] See *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

[19] See Rodriguez EM, Staffa JA, Graham DJ, 2001, *The role of databases in drug postmarketing surveillance*, Pharmacoepidemiology and Drug Safety, 10:407-10.

[20] In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria, and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the "real world" and randomized trials. The *Premarketing Guidance* discusses a number of types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

A. Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover, or other models.[21] The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse

[21] *Guidelines for Good Pharmacoepidemiology*, , International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/resources/guidelines_08027.cfm)

event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing (e.g., to study the natural history of disease or patterns of product use, or to estimate background rates for adverse events).

For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10,000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event–product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study.[22] Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

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[22] See, for example, Strom BL (ed), 2000, *Pharmacoepidemiology*, 3rd edition, Chichester: John Wiley and Sons, Ltd; Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology: An Introduction*, 3rd edition, Cincinnati, OH: Harvey Whitney Books.

There are a number of references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations,[23] and providing guidelines to facilitate the conduct, interpretation, and documentation of such studies.[24] Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes:

1. Clearly specified study objectives;
2. A critical review of the literature; and
3. A detailed description of the research methods, including:
   - the population to be studied;
   - the case definitions to be used;
   - the data sources to be used (including a rationale for data sources if from outside the U.S.);
   - the projected study size and statistical power calculations; and
   - the methods for data collection, management, and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. Demographic characteristics of patients enrolled in the health plans (e.g., age, geographic location);

2. Turnover rate of patients in the health plans;

3. Plan coverage of the medications of interest;

4. Size and characteristics of the exposed population available for study;

5. Availability of the outcomes of interest;

6. Ability to identify conditions of interest using standard medical coding systems (e.g., International Classification of Diseases (ICD-9)), procedure codes or prescriptions that could be used as markers;

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[23] Ibid.

[24] *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/resources/guidelines_08027.cfm).

7. Access to medical records; and

8. Access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

B. Registries

The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."[25] Whenever possible, a control or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest).[26]

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.[27] Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases; and

2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved, or when there is a need to evaluate

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[25] See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at http://www.ncvhs.hhs.gov.

[26] See for example, FDA Guidance for Industry, *Establishing Pregnancy Exposure Registries*, August 2002 http://www.fda.gov/cder/guidance/3626fnl.pdf.

[27] Ibid.

safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. The types of additional risk information desired;
2. The attainability of that information through other methods; and
3. The feasibility of establishing the registry.

Sponsors electing to initiate a registry should develop written protocols that provide: (1) objectives for the registry, (2) a review of the literature, and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of: (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management, and analysis, and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and we encourage sponsors to discuss their registry development plans with FDA.

C. Surveys

Patient or health care provider surveys can gather information to assess, for example:

1. A safety signal;

2. Knowledge about labeled adverse events;

3. Use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist;

4. Compliance with the elements of a RiskMAP (e.g., whether or not a Medication Guide was provided at the time of product dispensing); and [28]

5. Confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including: (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management, and analysis.[29] FDA recommends that a survey-based monitoring

[28] For a detailed discussion of RiskMAP evaluation, please consult the *RiskMAP Guidance*.

[29] See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

system include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g., from preclinical or other sources), FDA suggests that a sponsor consider further study (e.g., observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from preclinical findings to current observations. This submission should include the following:

1. Spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;

2. Background rate for the event in general and specific patient populations, if available;

3. Relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies;

4. Biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;

5. Safety findings from controlled clinical trials; and

6. General marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provide an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations, and, if appropriate, (1) propose steps to further investigate the signal through additional studies, and (2) propose risk

minimization actions.[30] FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class) and will communicate its conclusions to the sponsor whenever possible. Factors that are typically considered include:

1. Strength of the association (e.g., relative risk of the adverse event associated with the product);
2. Temporal relationship of product use and the event;
3. Consistency of findings across available data sources;
4. Evidence of a dose-response for the effect;
5. Biologic plausibility;
6. Seriousness of the event relative to the disease being treated;
7. Potential to mitigate the risk in the population;
8. Feasibility of further study using observational or controlled clinical study designs; and
9. Degree of benefit the product provides, including availability of other therapies.

As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps.[31] FDA recommends that assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket requirements under the FDCA and FDA implementing regulations) is sufficient for postmarketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A

[30] In the vast majority of cases, risk communication that incorporates appropriate language into the product's labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the *RiskMAP Guidance* for a complete discussion of RiskMAP development.

[31] For additional discussion of the relationship between risk assessment and risk minimization, please consult the *RiskMAP Guidance*.

pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.[32] The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;

2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);

3. The severity of the event;

4. The nature of the population(s) at risk;

5. The range of patients for which the product is indicated (broad range or selected populations only); and

6. The method by which the product is dispensed (through pharmacies or performance linked systems only).[33]

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP), as described in the *RiskMAP Guidance*. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.

FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for postmarketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious safety risks have been identified pre- or post-approval, or (2) at-risk populations have not been adequately studied.

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[32] As used in this document, the term "pharmacovigilance plan" is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a "pharmacovigilance plan" would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

[33] For a detailed discussion of controlled access systems, please consult the *RiskMAP Guidance*.

Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports);

2. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);

3. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure);

4. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs (see section V);

5. Creation of registries or implementation of patient or health care provider surveys (see section V); and

6. Additional controlled clinical trials.[34]

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks: (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question, or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. While additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g., through labeling) to minimize the risk to users of the product.

[34] For a discussion of risk assessment in controlled clinical trials, please consult the *Premarketing Guidance.*

EXHIBIT 14

Guidance

Drug Safety Information – FDA's Communication to the Public

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Drug Safety

TABLE OF CONTENTS

Contains Non-binding Recommendations

Guidance[1]
Drug Safety Information – FDA's Communication to the Public

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

I. WHAT IS THIS GUIDANCE ABOUT?

This document provides guidance on how FDA is developing and disseminating information to the public regarding important drug safety issues, including emerging drug safety information.[2] As discussed in more detail below, an *important drug safety issue* is one that has the potential to alter the benefit/risk analysis for a drug in such a way as to affect decisions about prescribing or taking the drug. The term *emerging drug safety information* refers to information about an important drug safety issue that has not yet been fully analyzed or confirmed.

For many years, FDA has provided information on drug risks and benefits to healthcare professionals and patients when that information has generated a specific concern or prompted a regulatory action, such as a revision to the drug product's labeling. More recently, FDA has begun taking a more comprehensive approach to making information on potential drug risks available to the public earlier, in some cases while the Agency still is evaluating whether any regulatory action is warranted. FDA believes that timely communication of important drug safety information will give healthcare professionals, patients, consumers, and other interested persons access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed individual treatment choices.

This Guidance[3] describes FDA's current approach to communicating important drug safety information, including emerging drug safety information, to the public and the factors that influence when such information is communicated. FDA may disseminate important drug safety information by other methods and at other times than those described in this guidance.

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[1] This guidance has been prepared by the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] The term *drug* as used in this guidance includes all drug and biological products regulated by CDER. Information about marketed drugs available on the Index to Drug-Specific Information Web page may include approved drugs used for labeled or unlabeled indications, or unapproved drugs.

[3] The draft version of this guidance was called *FDA's 'Drug Watch' for Emerging Drug Safety Information.*

II. WHY IS FDA ISSUING THIS GUIDANCE?

FDA has been reexamining its risk communication program, including how and when we communicate emerging drug safety information to the public. We are issuing this guidance to reaffirm our commitment to communicating important information about drug safety in a timely manner, in some cases while the Agency still is evaluating whether any regulatory action is warranted.

FDA's risk communication efforts are part of a larger drug safety initiative that began in November 2004, when FDA announced an initiative to strengthen the safety program for marketed drugs. This initiative included: (1) sponsoring an independent study by the Institute of Medicine of the National Academies of the effectiveness of the drug safety system, with emphasis on postmarketing risk assessment and surveillance; (2) conducting workshops and Advisory Committee meetings regarding complex drug safety and risk management issues, including emerging concerns; and (3) publishing three risk management guidances.[4]

FDA augmented its drug safety initiative in February 2005 by creating an independent Drug Safety Oversight Board to enhance oversight of drug safety decision making within CDER. FDA also announced its commitment to "increase the transparency of the Agency's decision-making process by establishing new and expanding existing communication channels to provide targeted drug safety information to the public. These channels will be used to help ensure that established and emerging drug safety data are quickly available in an easily accessible form. The increased openness will enable patients and their healthcare professionals to make better-informed decisions about individual treatment options."[5]

To fulfill this commitment, FDA issued for comment a draft guidance titled *FDA's 'Drug Watch' for Emerging Drug Safety Information* in May 2005. In December 2005, FDA held a public hearing regarding "FDA's Communication of Drug Safety Information" that examined the various risk communication tools employed by FDA. Comments from participants emphasized that, increasingly, patients are taking a more active role in their healthcare. Patients want information about the drugs they are taking, and actively seek this information from various sources, including the Internet. Patients and their healthcare providers rely on information from these sources to make important prescribing and treatment decisions (including about consumer self-care). Because of its expertise and access to important information concerning the benefits and safety of medications, FDA is an important source of drug information.

FDA has carefully reviewed the comments it received on the draft guidance (30 comments were submitted to the public docket)[6] and during the public hearing. This final version of the guidance reflects our consideration of these comments, as well as our experience with posting emerging drug safety information.

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[4] See the following guidance documents published in March 2005: *Premarketing Risk Assessment*; *Development and Use of Risk Minimization Action Plans*; and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, available at http://www.fda.gov/cder/guidance/index.htm.

[5] FDA Fact Sheet (February 15, 2005).

[6] See Docket No. 2005D-0062 (available at http://www.fda.gov/ohrms/dockets/dockets/05d0062/05d0062.htm).

Due to potential confusion between the proposed *Drug Watch* and FDA's existing *MedWatch* program, FDA no longer plans to use the name *Drug Watch* to describe the Web page that contains drug safety information. As discussed in more detail in section VII of this guidance, we have identified drugs that have been the subject of a Public Health Advisory or an Alert (see section VI.E of this guidance) on a single Web page linked from FDA's Web site. This is part of our ongoing effort to use and enhance existing FDA communications mechanisms to better convey important drug safety information to the public. In addition, we have revised this guidance to describe the various methods FDA currently uses to communicate established and emerging drug safety information to the public. It should be noted that we will continue to evaluate and enhance the effectiveness of the various methods we use to communicate about important drug safety issues, including the mechanisms described in this guidance and the presentation of drug safety information on the Agency's Web sites (http://www.fda.gov and http://www.fda.gov/cder). We intend to update this guidance, as appropriate, to reflect any substantial modifications to our communication of drug safety information to the public.

III. WHAT DRUG SAFETY INFORMATION DOES FDA COMMUNICATE?

FDA communicates information about *important drug safety issues*, and under the drug safety initiative, FDA has enhanced its efforts to communicate such information earlier in our decision making process (see section V of this guidance). An *important drug safety issue* is one that has the potential to alter the benefit/risk analysis for a drug in such a way as to affect decisions about prescribing or taking the drug. Examples of important drug safety issues include, but are not limited to:

- Serious adverse drug experiences[7] identified after approval or in the setting of a new use
- Additional serious or more frequent adverse drug experiences in a subpopulation of patients
- Medication errors

[7] A *serious adverse drug experience* is defined as:

> Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

(21 CFR 314.80(a)).

IV. HOW DOES FDA EVALUATE DRUG SAFETY INFORMATION?

All drugs have risks, and healthcare professionals and patients must balance the risks and benefits of a drug when making decisions about medical therapy. FDA monitors and reviews available safety information related to marketed drugs throughout each drug product's lifecycle. When a drug is approved, the product labeling includes, among other things, available information about the benefits and risks of the drug. After drug approval, the Agency may learn of new, or more frequent, serious adverse drug experiences from postapproval clinical studies or from clinical use. For example, additional adverse drug experiences, some of them serious, may be identified as a drug is used more widely and under more diverse conditions (e.g., concurrently with other drugs), or as the drug is prescribed for off-label uses.

As new information related to a marketed drug becomes available, the Agency reviews the data and evaluates whether there is a potential drug safety concern. When a potential drug safety concern arises, relevant scientific experts within the Agency engage in a prompt review and analysis of available data. Often, there is a period of uncertainty while FDA evaluates the new safety information to determine whether there is an important drug safety issue related to a specific drug or drug class and whether regulatory action is appropriate. During this period, FDA also is actively engaged in scientific efforts to gather additional safety information. The Drug Safety Oversight Board may be consulted and provide recommendations to the Director of the Center for Drug Evaluation and Research regarding the management and communication of an emerging drug safety issue. FDA also may consult an Advisory Committee regarding an emerging drug safety issue. Sponsors are also evaluating the new safety information and providing the results of their analyses to FDA during this time. As additional data relevant to an emerging drug safety issue become available (e.g., data from an ongoing study or data from available clinical databases), such data are considered in the analysis and decision-making process. Upon evaluation of additional data, further regulatory action, such as a revision to product labeling or a Risk Minimization Action Plan (RiskMAP), may be appropriate.

Interpretation of postmarketing safety data is complex, involving analysis of postapproval clinical data, detailed review of adverse drug experience reports in the context of relevant clinical studies, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information. Decisions about how to address a safety concern often are a matter of judgment, about which reasonable persons with relevant expertise may disagree. We engage in vigorous and comprehensive discussions within the Agency regarding potential drug safety issues to ensure that all points of view are considered prior to making a decision on how to proceed.

As the Agency evaluates a drug safety issue to determine whether regulatory action is warranted, we may communicate further information to the public at appropriate points in the decision-making process. Consistent with our public health mandate, we may advise the public of an emerging drug safety concern as well as the next steps the Agency may take regarding an important drug safety issue.

V. WHEN DOES FDA COMMUNICATE EMERGING DRUG SAFETY INFORMATION?

We use the term *emerging drug safety information* to describe information FDA is monitoring or analyzing that may have the potential to alter the benefit/risk analysis for a drug in such a way as to affect decisions about prescribing or taking the drug (i.e., an important drug safety issue), but that has not yet been fully analyzed or confirmed. Emerging drug safety information may be derived from data from postmarketing surveillance (for example, reported serious adverse drug experiences), clinical studies, clinical pharmacology studies, epidemiological studies, or the scientific literature. Such information may relate to new risks or new information on known risks.

For years, FDA and sponsors have disseminated emerging drug safety information. The Agency currently disseminates emerging drug safety information after having completed an analysis of available data and, in some cases, before having reached a decision about the need for a regulatory action. Agency communications about emerging drug safety information may help achieve certain longstanding public health goals, including enhanced vigilance on the part of healthcare professionals who may be prompted by the information to increase their reporting of safety observations to FDA. We are mindful of the potential public health implications of providing emerging drug safety information and are particularly concerned about possible consequences, such as inappropriate modification or discontinuation of useful treatment. We attempt to anticipate and address these possible consequences through our risk communications by describing the nature of a safety concern and what is known about its relationship to a particular drug and making recommendations for healthcare professionals and patients about how to monitor for and manage the concern. There will always be some tension between the goal of having people informed about potentially important information as early as possible and the goal of having that information thoroughly substantiated. Our goal is to make emerging drug safety information available to the public in a balanced, impartial manner so that healthcare professionals and patients can consider the information when making decisions about medical treatment despite uncertainties in the data. The Agency is committed to providing accurate, clear, reliable, and useful drug safety information.

FDA considers many factors in the course of evaluating an emerging drug safety concern and deciding whether emerging drug safety information should be made available to the public. These factors include, but are not limited to, the following:

- Reliability of the data
- Magnitude of the risk
- Seriousness of the event (e.g., severity and reversibility) relative to the disease being treated
- Plausibility of a causal relationship between the use of a drug and the adverse event[8]
- Extent of patient exposure (e.g., how broadly is the drug used)
- Potential to prevent or mitigate the risk in the patient population (e.g., monitoring)
- Effect on clinical practice
- Disproportionate impact on particular populations (e.g., children or the elderly)

[8] See, e.g., guidance for industry on *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* at pages 6 to 7 and 17 to 18.

Providing information about an emerging drug safety issue does not necessarily mean that FDA has concluded there is a causal relationship between the drug and the adverse events described. Communicating emerging drug safety information also does not necessarily mean that FDA is advising healthcare professionals to limit their prescribing of the drug at issue, rather it is intended to further inform such prescribing.

VI. HOW DOES FDA COMMUNICATE IMPORTANT DRUG SAFETY INFORMATION?

FDA uses a broad range of methods to communicate drug safety information to the public. Certain forms of communication are targeted to specific audiences (e.g., healthcare professionals or patients). Others are directed at more than one group to ensure widespread dissemination of information about important drug safety issues, including emerging drug safety issues. FDA is continuing to evaluate its communication efforts and will modify them to enhance their accessibility and effectiveness. We welcome public comment at any time suggesting ways to improve our safety communications. The table, below, summarizes the methods discussed in this section for FDA communication of drug safety information.

Table: Summary of Selected Methods for FDA Communication of Drug Safety Information

Type of Communication	Content	Target Audience
Professional labeling for prescription drugs	Summary of essential information needed for safe and effeetive use of the drug.	Healthcare providers
Patient-directed labeling for prescription drugs (patient package inserts and Medication Guides)	Summary of essential information needed for safe and effective use of the drug.	Patients
OTC "Drug Facts" labeling	Summary of essential information needed for safe and effective use of the drug.	Consumers
Public Health Advisory	Information and advice regarding an emerging drug safety issue or other important public health information.	General public
Patient Information Sheet	Concise summary in plain language of the most important information about a particular drug. Includes an Alert when appropriate to communicate an important, and often emerging, drug safety issue.	Patients and/or consumers, lay caregivers, and interested members of the general public
Healthcare Professional Sheet	Concise summary of an important, and often emerging, drug safety issue, with background information about the detection of the issue and points to consider for clinical decision making.	Healthcare professionals
Alerts on Patient Information and Healthcare Professional Sheets	Summary of an important, and often emerging, drug safety issue. Alerts are tailored to the needs of the primary target audience for each type of information sheet.	Healthcare professionals, patients and/or consumers, lay caregivers, and interested members of the general public

A. Labeling (including patient package inserts and Medication Guides)

FDA-approved drug product labeling is the primary source of information about a drug's safety and effectiveness, and it summarizes the essential scientific information needed for the safe and effective use of the drug. Compliance with the recently issued physician labeling rule[9] for prescription drugs is expected to further enhance the usefulness of product labeling and further facilitate the safe and optimal use of prescription drugs.

Labeling for prescription drug products is directed to healthcare professionals, but may include sections that are intended for patients and that also must be FDA-approved. For some prescription drugs, such as oral contraceptives and estrogens, FDA long ago determined that the safe and effective use of the drug required additional labeling in nontechnical language to be distributed directly to patients by their healthcare provider or pharmacist (21 CFR 310.501 and 310.515). These *patient package inserts* also may be provided voluntarily by manufacturers for other drugs and are regulated by FDA as product labeling.

More recently, when patient-directed labeling was considered necessary for proper use of a drug, FDA has required patient labeling in nontechnical language in the form of Medication Guides (MedGuides). These have been required for certain prescription drugs that pose a serious and significant public health concern and for which FDA-approved patient information is necessary for a patient's safe and effective use of the product. MedGuides are required if FDA determines that one or more of the following circumstances exists:

- Patient labeling could help prevent serious adverse effects.
- A drug product has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect a patient's decision to use, or to continue to use, the product.
- A drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.[10]

Finally, over-the-counter (OTC) drugs bear a *Drug Facts* label that conveys information in a clear, standardized format to enable patient self-selection of an appropriate drug and enhance the safe and effective use of the drug by consumers.[11]

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[9] Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 FR 3922 (January 24, 2006). For further information, see http://www.fda.gov/cder/regulatory/physLabel/default.htm.

[10] See 21 CFR 208.1.

[11] See 21 CFR 201.66 (format and content requirements for over-the-counter (OTC) drug product labeling).

B. Public Health Advisories

FDA issues Public Health Advisories (PHAs) to provide information regarding important public health issues to the general public, including patients and healthcare professionals. For example, PHAs may:

- Highlight important safety information about a drug
- Inform the public about the status of FDA's evaluation of an emerging drug safety issue
- Announce the implementation of a RiskMAP for a drug
- Advise the public regarding a manufacturer's suspension of marketing of a drug due to safety concerns
- Provide other important public health information

Emerging drug safety information has been disseminated in PHAs for many years, and such PHAs may include recommendations to mitigate a potential risk. PHAs often are issued in conjunction with other drug safety communications, such as Alerts on Patient Information Sheets and Healthcare Professional Sheets (see next sections). PHAs are available through the CDER Web site and disseminated via the MedWatch Partners Program.

C. Patient Information Sheets

In 1998, FDA began posting Information Sheets for consumers following approval of drugs that are new molecular entities (i.e., contain an active ingredient not previously marketed in the United States). These communications convey, in plain language, important information for consumers contained in a drug product's approved labeling about the safe and effective use of the drug. In 2005, FDA began posting Patient Information Sheets when important new information regarding the safety of a marketed drug came to the attention of the FDA.[12] Patient Information Sheets include an Alert (see section below on Alerts) when appropriate to communicate an emerging drug safety issue. These Information Sheets can be found on the FDA's Index to Drug-Specific Information, currently at http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.

Patient Information Sheets encourage patients to talk with their healthcare providers for further information. Patient Information Sheets also provide telephone and e-mail contact information for FDA's Drug Information line to address specific questions. FDA continues to collect input on the usefulness of these consumer communications through feedback mechanisms, such as focus groups, surveys, and public meetings, and anticipates that these consumer communications will continue to evolve.

[12] Information Sheets for consumers developed to communicate information about drugs that are new molecular entities previously have been titled "Consumer Information Sheets" and are transitioning to the Patient Information Sheet format. References to Patient Information Sheets in this Guidance should be interpreted to include Consumer Information Sheets, as appropriate.

D. Healthcare Professional Sheets

Healthcare Professional Sheets provide a summary of important, and often emerging, drug safety information for a particular drug or drug class and also can be found on the FDA's Index to Drug-Specific Information. Healthcare Professional Sheets begin with a summary Alert paragraph (see section below on Alerts) followed by more detailed sections explaining the Alert, including clinical considerations or recommendations for the healthcare professional, a summary of the data, and, when applicable, implications of the Alert.

Healthcare Professional Sheets are intended to provide adequate factual information to address potential questions from patients and facilitate a healthcare professional's consideration of the drug safety issue. As with the Patient Information Sheets, FDA continues to collect input on the usefulness of these communications through a variety of feedback mechanisms and anticipates that healthcare professional communications will continue to evolve.

E. Alerts on Patient Information and Healthcare Professional Sheets

When FDA becomes aware of emerging information on a potentially important drug safety issue and we determine patients and healthcare professionals should know about the information while we continue our evaluation, we currently provide this information in Patient Information Sheets and Healthcare Professional Sheets as an *Alert*. Alerts also may be used to highlight important new information in product labeling or an important change in a risk management program. For example, an Alert may describe:

- Newly observed, serious adverse events that may be associated with use of a drug
- Information about how such serious adverse events might be prevented by appropriate patient selection, monitoring of patients, or use or avoidance of the therapy
- Information regarding a serious adverse event that FDA believes may be associated with use of a drug in populations in whom the drug was not previously studied

In some cases, an Alert and/or other safety communication may comment on an international regulatory agency action with respect to a drug also marketed in the United States or on published literature reporting a new safety-related finding regarding a marketed drug.

The essential information in the Alert should not differ between the Patient Information Sheets and Healthcare Professional Sheets, although we may clarify technical terms on the Patient Information Sheets to enhance consumer understanding and provide more detailed information for healthcare professionals in the Healthcare Professional Sheets.

An Alert is clearly identified along with a statement that reflects the stage of the analysis with respect to regulatory decision making or other potential limitations on the interpretation of the safety information. For example, a statement regarding emerging drug safety information may advise the following:

> This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging drug safety issue. Nor does it mean that FDA is advising practitioners to discontinue prescribing the product. FDA is considering, but has not reached a conclusion about, whether this information warrants any regulatory action. FDA intends to provide updated information when it becomes available.

As noted in section V above, our goal is to make emerging drug safety information available to the public in a balanced, impartial manner so that healthcare professionals and patients can consider the information when making decisions about medical treatment despite uncertainties in the data. The Agency is committed to providing accurate, clear, reliable, and useful drug safety information.

F. Other Methods of Communication

Consistent with the Agency's commitment to the expansion of existing communication channels to provide targeted drug safety information to the public, FDA is exploring various methods of communication, including concise advisories and other Internet postings, more detailed short articles, and background papers. In addition to written communications, FDA is assessing other communication tools, including broadcasts and conference calls to disseminate drug safety information. If new communication tools are adopted, we intend to update this guidance, if appropriate.

Sponsors also use various methods to communicate drug safety information. For example, a sponsor may distribute a "Dear Healthcare Professional" letter (sometimes referred to as a "Dear Doctor" letter) to convey important information regarding a marketed drug. A sponsor may issue a Dear Healthcare Professional letter on its own initiative or following a request by FDA. Dear Healthcare Professional letters may be used to disseminate information regarding a significant hazard to health, to announce important changes in product labeling, or to emphasize corrections to prescription drug advertising or labeling.

VII. WHERE CAN I FIND FDA'S DRUG SAFETY INFORMATION?

All of the various forms of drug safety communications described in the preceding section currently are available via links found on the FDA Web site (e.g., links to the Index to Drug-Specific Information Web page, Drugs@FDA, and MedWatch Web pages). FDA's Web site provides an easily accessible link to the Index to Drug-Specific Information Web page (currently at http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm) from which the public may access information about drugs that are the subject of a Public Health Advisory and/or an Alert regarding an important, and often emerging, drug safety issue, as well as established drug safety information. This

Index contains links to available Drug Information Pages for specific drugs (identified by both trade name and nonproprietary name), which contain approved drug product labeling, consumer-friendly Information Sheets, and other drug information. Drug Information Pages generally are available for drugs that (1) are new molecular entities; (2) have existing Consumer or Patient Information Sheets, Healthcare Professional Sheets, or other consumer information materials; or (3) have been the subject of recent safety communications. Drugs that have an active FDA safety alert are identified by an asterisk. For drugs without a Drug Information Page, the Web page links consumers to Drugs@FDA, which contains drug product labeling and other regulatory information related to approved drugs (see http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

Safety information regarding medical products (including drugs, biologics, devices, and dietary supplements), such as Dear Healthcare Professional letters, Public Health Advisories, Press Releases, and market withdrawals, also is available through MedWatch Safety Alerts. The MedWatch program augments FDA and manufacturer communication of drug safety information by distributing MedWatch Safety Alerts to individual subscribers and through its MedWatch Partners Program. This information is available to the general public on the MedWatch Web site (http://www.fda.gov/medwatch/safety), which contains archived information dating back to 1996.

VIII. HOW WILL FDA HANDLE CONFIDENTIAL INFORMATION?

Most of the information currently posted on the Index to Drug-Specific Information Web page is information that is now made available to the public pursuant to Freedom of Information Act (FOIA) requests. Because of the importance of emerging drug safety information to healthcare professionals and patients, FDA has decided to take steps to make such information available, after proper redaction of confidential commercial and personal privacy information, without waiting for a FOIA request. Information will be posted in accordance with applicable disclosure laws and FDA regulations.

IX. HOW WILL DRUG SAFETY INFORMATION BE UPDATED?

As already explained, we have established a Drug Safety Oversight Board (DSB) which is responsible for making recommendations to the Director of the Center for Drug Evaluation and Research (CDER) about the management of emerging drug safety issues. The DSB is supported by a staff that coordinates CDER's communication efforts regarding emerging drug safety information.

The public can access the most current safety information about a drug through the Index to Drug-Specific Information Web page. FDA intends to update the information available on this Web page on a periodic basis to reflect new information that becomes available.

Emerging drug safety information presented as Alerts is identified by the month and year in which the information is posted on the Index to Drug-Specific Information Web page. We intend to update Alerts on Patient Information Sheets and Healthcare Professional Sheets to describe important new information relevant to the emerging drug safety issue, or remove Alerts after the

emerging drug safety issue is addressed through revision of product labeling, restricted distribution, request for voluntary withdrawal from the market, or other regulatory action. Once an emerging safety issue has been addressed through regulatory action or a decision that the emerging safety concern is not an important drug safety issue, we intend to modify and/or archive the Patient Information Sheet, Healthcare Professional Sheet, and other communications on our Web site. We intend to make this information available via a link to historical information as follows:

> *Patient Information Sheets:* If the emerging drug safety issue has been addressed by a revision to product labeling, we intend to remove the Alert and incorporate the updated labeling information into the Patient Information Sheet.
>
> *Healthcare Professional Sheets:* To ensure continuity following resolution of an Alert that results in a revision to product labeling, we intend to keep the Healthcare Professional Sheets available on the Drug Safety Web site until the revised product labeling is widely available. Thereafter, we intend to archive the Healthcare Professional Sheets on our Web site.
>
> *Public Health Advisories:* Following a determination of whether regulatory action is appropriate to address the emerging drug safety issue, we intend to archive on our Web site the Public Health Advisories related to the safety concern.

Some important drug safety information may have utility independent of any regulatory action. For example, sometimes a sponsor may agree to conduct a long-term study related to an emerging drug safety issue. In such instances, the drug safety information may remain posted until the issue is resolved.

FDA recognizes that resolution of some emerging drug safety issues may not be accomplished in the short term. This may be attributable to the complexity of an issue or the need for clinical studies of adequate duration to evaluate a potential risk with a long latency period. In such cases, we intend to maintain the emerging drug safety information on safety communications such as Patient Information Sheets and Healthcare Professional Sheets pending resolution of the safety issue, and plan to update them as appropriate to reflect continuing evaluation of the issue. This will ensure that important unresolved safety issues that may affect a healthcare professional's decision to prescribe, or a patient's or consumer's decision to use, a medication continue to be communicated. We plan to identify updated information with the month and year in which it was added to the Web site or communicated by other methods.

If data become available that provide sufficient evidence that a drug is not associated with the safety concern previously described by the Agency as an emerging drug safety issue, FDA intends to update the Alert accordingly. In such instances, FDA plans to revise safety communications such as Patient Information Sheets and Healthcare Professional Sheets to provide an update of comparable prominence to reflect this new information. We intend to keep this revised information on the Web site for an appropriate period following publication of the update resolving the safety issue.

X. WHAT INTERACTIONS WILL FDA HAVE WITH SPONSORS BEFORE COMMUNICATING EMERGING DRUG SAFETY INFORMATION TO THE PUBLIC?

FDA intends to notify the relevant sponsor that emerging drug safety information about its drug will be posted on the FDA Web site at least 24 hours before the first instance in which emerging information about that drug is communicated. Our communication of emerging drug safety information is intended to represent FDA's independent analysis of emerging information and FDA's scientific judgment as to the appropriate communication of this emerging drug safety information to the public. FDA may solicit sponsor input when appropriate; for example, to confirm the accuracy of factual information.

For purposes of this guidance, the relevant sponsor generally is the NDA or ANDA holder for the drug that is the subject of a Patient Information Sheet or Healthcare Professional Sheet containing an Alert or a Public Health Advisory regarding an important drug safety issue. We recognize that OTC drugs subject to one or more final OTC monographs, rather than approved pursuant to an NDA or ANDA, may be manufactured by multiple entities and, thus, have multiple relevant sponsors. FDA continues to consider appropriate mechanisms to facilitate timely notification of affected entities marketing OTC drugs and welcomes comment on this issue.

Sponsors are required to report certain adverse drug experience information to FDA in accordance with our regulations[13] and may provide the Agency with additional information relevant to a drug safety issue at any time. A sponsor also may request that the Agency update its communication of emerging drug safety information if the sponsor provides additional information supporting the request.[14]

XI. HOW WILL THE COMMUNICATION OF DRUG SAFETY INFORMATION AFFECT THE PROMOTION OF PRESCRIPTION DRUGS?

FDA recognizes that some sponsors may consider making promotional comparisons between their drugs and drugs for which emerging drug safety information has been provided by the Agency. We remind sponsors that all safety and effectiveness claims made in prescription drug promotion,[15] including claims based on government materials available from the Index to Drug-Specific Information, must be supported by substantial evidence or substantial clinical experience and must not be otherwise false or misleading (21 U.S.C. 355 and 352; 21 CFR 202.1(e)).

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[13] Sponsors of approved NDAs or ANDAs, manufacturers of marketed prescription drugs for human use without approved NDAs or ANDAs, and licensed manufacturers of approved biologic product license applications are required to report adverse experiences to the FDA under 21 CFR 310.305, 314.80, 314.98, and 600.80.

[14] Any such request should be made in accordance with standard procedures for submitting information concerning a particular drug to the Agency (e.g., directed to the appropriate division within the Office of New Drugs, the Office Generic Drugs, or the Office of Nonprescription Products, as appropriate).

[15] The Federal Trade Commission (FTC) has primary responsibility for regulating the advertising of nonprescription drug products.

Neither the fact that the Agency has communicated emerging drug safety information for a drug nor the specific information posted about that drug will generally constitute (either separately or collectively) substantial evidence or substantial clinical experience that would support a comparative safety or effectiveness claim. Therefore, comparative claims made in prescription drug promotion based on an Agency communication of emerging drug safety information (e.g., "Our drug is safer because of the emerging drug safety information posted by the FDA about a competitor's drug") may be considered false or misleading.

Representations that minimize the implications of emerging drug safety information communicated by the Agency also may be considered false or misleading. For those seeking to explain to healthcare professionals what emerging drug safety information means, we refer to the sections of this guidance that discuss the purpose of disseminating emerging drug safety information and the nature of the information to be posted on the Index to Drug-Specific Information Web page.

EXHIBIT 15

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

ANDREW C. von ESCHENBACH, M.D.
COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

UNITED STATES HOUSE OF REPRESENTATIVES

June 6, 2007

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Andrew von Eschenbach, M.D., Commissioner of Food and Drugs at the United States Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to participate in this hearing regarding FDA's assessment of the safety of rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl), a drug approved to improve glycemic control in patients with type 2 diabetes.

I would like to frame my testimony this morning by placing it in the context of the very important and complex societal challenge of providing abundant and timely information to patients and health care professionals, while at the same time making regulatory decisions that affect the availability and use of life-saving or health-enhancing interventions.

I. DRUG SAFETY: A RISK-TO-BENEFIT BALANCE

FDA has a strong record on issues of safety and remains the world's gold standard for drug regulation. In reflecting on the concept of drug safety, it is important to remember that no drug is absolutely safe and to recognize that sometimes information about the safety of a drug emerge after the drug is on the market. FDA approves a drug only after a sponsor demonstrates that the drug's benefits outweigh its risks for a specific population and a specific indication, and shows that the drug meets the statutory standard for safety and effectiveness. Because of practical limitations on how many patients can be studied for any given drug, the full array of potential risks does not necessarily always emerge during the mandatory clinical

trials conducted before approval. Indeed, serious adverse effects may occasionally emerge after approval through post-marketing clinical trials or through spontaneous reporting of adverse events or both.

FDA's role as a public health agency is to protect and promote the nation's health by assuring that patients and health care providers have access to safe and effective drugs along with accurate benefit and risk information to make informed choices. The issue of how to identify and, when possible, limit adverse reactions is challenging. How to weigh the impact of reported adverse reactions against known benefits of the products for individual patients and the public health is multifaceted and complex, involving scientific as well as public policy issues. As described below, FDA has approached the issues associated with the diabetes drug, rosiglitazone, mindful of our important role as a public health agency, and the need to make the best regulatory decisions we can for health care providers and patients.

II. ROSIGLITAZONE AND THE TREATMENT OF TYPE 2 DIABETES

As a science-based regulatory agency, FDA bases its regulatory decisions on sound science. More than that, FDA's decisions must result from a comprehensive, rigorous, disciplined analysis of all the science and data that bear on the evidence. This is precisely the process that FDA followed with regard to rosiglitazone, and I would like to outline that process for you.

FDA approved Avandia in 1999 for treatment of Type 2 diabetes, a serious and life threatening disease that affects about 18 to 20 million Americans. Diabetes is a leading cause

of blindness, kidney failure, and limb amputation, and a major contributor to coronary heart disease.

Since the approval of rosiglitazone in 1999, numerous clinical studies have examined how well rosiglitazone works relative to other diabetes drugs individually and in combination. These studies, described in more detail below, have also shed new light on some of the safety concerns associated with this product. Since the drug was approved, FDA has been monitoring several heart-related adverse events (e.g., fluid retention, edema, and congestive heart failure [CHF]) based on signals seen in these controlled clinical trials and from post-marketing reports.

FDA has updated the product's labeling on several occasions to reflect these new data. In April 2006, the labeling for Avandia was updated to include new data in the WARNINGS section about a potential increase in heart attacks and heart-related chest pain in some patients. This change was based on the results of a controlled clinical trial in patients with existing CHF. In the study, diabetic patients with known, mild CHF were randomized to receive either placebo or rosiglitazone. A higher number of heart attacks or angina was observed in patients treated with rosiglitazone compared to those treated with placebo. The difference was not statistically significant, but we considered the information to be clinically important, and it was therefore included in labeling.

In August 2006, the manufacturer of Avandia, GlaxoSmithKline (GSK or the company), provided FDA with a pooled analysis (meta-analysis) of 42 separate double-blinded,

randomized, controlled clinical trials to assess the efficacy of rosiglitazone for treatment of type 2 diabetes compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. At the same time, the company also provided a population-based database study discussed below. The pooled analysis and the population-based database study presented inconsistent data with regard to the potential cardiovascular risk of rosiglitazone. Since then, results of other long-term controlled clinical studies have been published or unpublished results have been made available to FDA. In looking at all the studies to date related to the potential contribution of rosiglitazone to increasing the risk of heart attack, the data are inconsistent and conclusions are not clear.

III. COMMUNICATING ABOUT POSSIBLE RISKS FROM MEDICAL PRODUCTS

FDA is committed to early communication of emerging information about the safety of medical products. But any communication must be responsible and measured, taking into account the impact that the message will have on patients and practitioners alike, to encourage good heath care choices, and help avoid bad ones.

The issues of whether using the diabetes drug rosiglitazone increases the risk of heart attacks, and how and what information should be communicated in the face of inconsistent evidence, illustrate the inherent tensions between early communication of emerging safety information and waiting to communicate information until after a comprehensive scientific assessment is completed and a regulatory decision is made. There are consequences in communicating safety concerns when FDA's safety assessment is still underway and before it has decided what, if any, regulatory action is appropriate. In light of a signal of concern in a diabetes

drug like rosiglitazone, patients may choose to unilaterally discontinue their treatment, despite advice from FDA and other medical experts not to do so. Discontinuation of any anti-diabetic therapy can result in loss of control of blood sugar, which carries risks of its own, including increased infections and blurred vision. Also, switching to another diabetes therapy does not necessarily ensure similar glycemic control for that individual patient. Moreover, other anti-diabetic drugs have their own specific safety concerns.

Let me describe FDA's public communication about the data submitted related to risk for heart attacks. FDA did not publicly discuss the data submitted by GSK at the time it was submitted in August 2006, because the data from the pooled analysis and the population based study were inconsistent and we began a comprehensive internal re-analysis of those data. On May 21, 2007, FDA issued a safety alert that addressed potential safety issues stemming from the pooled analysis of previously completed controlled clinical trials demonstrating a potentially significant increase in the risk of heart attack and heart-related deaths in patients taking this drug. Also, the FDA alert noted that other published and unpublished data from long-term controlled clinical trials of the drug did not show this type of risk and, in fact, provide inconsistent evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. We urged patients to consult with their health care providers about this information as they evaluated their treatment options. Also, on May 21, 2007, another meta-analysis of rosiglitazone studies, conducted by Dr. Stephen Nissen, was published in the New England Journal of Medicine (NEJM). FDA was not aware of Dr. Nissen's study methods or findings until the date of the publication. Dr. Nissen's analysis was based on data from 42 controlled clinical trials (though this is the same number of studies as in the GSK pooled

analysis, many-- but not all-- of the studies were the same). Despite the differences in the studies, the conclusions of Dr. Nissen and GSK about the estimated risk of cardiac ischemia from their respective studies were similar.

On May 23, 2007, consistent with recommendations made by senior FDA staff at an internal regulatory briefing held in April 2007, FDA issued letters to the manufacturers of Avandia and pioglitazone, (marketed as Actos) another drug in the same therapeutic class, requesting that the product labeling include a boxed warning to more prominently address the risks of congestive heart failure associated with the use of these drugs in certain patients. Although this issue is already prominent in the WARNINGS section for both drugs, FDA decided to make this request because, despite the existing warnings, these drugs were being prescribed to patients with significant heart failure. FDA will work diligently with both companies to accomplish these revisions.

On May 29, 2007, FDA held a Stakeholder Meeting to discuss the recent safety alert for rosiglitazone. Because we wanted to make sure that the nuanced message about rosiglitazone is both clearly articulated and reaches the right audience, we invited over forty organizations representing patients, health care professionals, and government agencies to participate.

In addition, FDA maintains current information about rosiglitazone for patients and health care professionals on its website. The posted information reflects FDA's current analysis of available data concerning this drug and does not mean that FDA has concluded there is a

causal relationship between the drug product and the emerging drug safety issue, nor does it mean that FDA is advising health care professionals to discontinue prescribing the product.

IV. NEXT STEPS

Even before Dr. Nissen's meta-analysis was made public, FDA was planning to convene an Advisory Committee meeting to allow a public discussion of the available data on rosiglitazone and to seek input from our expert advisors on how to interpret the large, and often inconsistent dataset. The Agency has decided to convene the Advisory Committee in the near future because we have serious concerns that patients on Avandia and their health care providers are confused about the safety of this drug as a result of media reports surrounding the recent NEJM publication. At a public Advisory Committee meeting, experts with specialties in diabetes and heart disease will review the entire set of data that FDA has received from the sponsor. FDA will ask the Committee to make recommendations and give the Agency guidance on additional regulatory action that could be taken.

V. BACKGROUND INFORMATION AND DATA

Evaluating the benefits and risks of all drug products is a dynamic process—and FDA's ongoing evaluation of rosiglitazone is no exception. FDA has received and is continuing to receive data from several different clinical studies of rosiglitazone for treatment of type 2 diabetes. These studies vary with respect to the study design (e.g., pooled analysis, meta-

analysis, individual randomized controlled clinical trial, and observational epidemiological study), patient populations enrolled, treatment groups, and length of patient follow-up.

Among the relevant studies we are aware of are two large, long-term clinical outcome studies (RECORD and BARI-2D) that are underway and nearing completion of patient follow up. Both of these studies may yield valuable information on rosiglitazone. In addition, two completed long-term studies have recently been published, DREAM (a study conducted by academic investigators, not GSK) and ADOPT (a Post-marketing Commitment study conducted by GSK). Both of these have published results. Their data are in the process of being analyzed in detail by FDA (ADOPT) or being obtained to allow this (DREAM). We are working to analyze, as quickly as possible, valuable data from these studies in order to better understand the risks and benefits of rosiglitazone. Following are summaries of the studies and data.

A. Clinical Trial Data - Pooled Analysis of 42 Studies

As previously noted, in August 2006, GSK, the manufacturer of Avandia provided FDA with a pooled analysis (meta-analysis) of 42 separate double-blinded, randomized controlled clinical trials to assess the efficacy of rosiglitazone for treatment of type 2 diabetes compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. The combined studies included 8,604 patients on rosiglitazone and 5,633 patients randomized to a variety of alternative therapeutic regimens, including placebo. In general, these studies had differing primary efficacy endpoints; they were not designed to thoroughly investigate cardiovascular safety. Treatment groups varied and included rosiglitazone alone or in

combination with insulin, sulfonylureas, and/or metformin. The comparator arms were varied and included placebo alone or as an add-on treatment to other anti-diabetic agents, and other active anti-diabetic treatment regimens. The combined patient population was diverse, including patients with average duration of diabetes ranging from 5 to 13 years as well as patients with significant risk factors for cardiovascular disease (e.g., history of myocardial infarction, bypass surgery, stroke, peripheral vascular disease, and New York Heart Association Class 1 and 2 heart failure). All but four studies were six months in duration or less.

In this pooled analysis as submitted by GSK, the overall incidence of myocardial ischemia in rosiglitazone-treated subjects relative to the comparators was 1.99 percent vs. 1.51 percent with a hazard ratio of 1.31 (95 percent CI 1.01-1.70). This risk equates to a more than 30 percent excess risk of myocardial ischemic events in rosiglitazone-treated patients. (This means that if this risk estimate were accurate and a patient's risk of having a heart attack in a given year were 2 percent, taking rosiglitazone would increase that risk to 2.6 percent. It does not mean that diabetics taking the drug have a 30 percent risk of having a heart attack). These data, if confirmed, would be of significant concern because patients with diabetes are already at an increased risk of heart disease. FDA scientists identified several substantial concerns with the methodology used by GSK in conducting their pooled analysis. GSK performed an analysis that pooled data on patients from 42 clinical trials of rosiglitazone administered as monotherapy and in combination with sulfonylureas, metformin and insulin and compared pooled results across these treatment groups. GSK pooled analysis assigned patients to exposure groups and in doing so did not maintain the randomized comparison of

treatment differences within each of the 42 studies and did not preserve the study identity for each patient as the unit of analysis. This approach is not the generally accepted way to meta-analyze many independent randomized studies and the consequence of their pooled approach was comparisons that are potentially biased and not interpretable. Given the potential importance of the finding of excess risk of ischemic cardiovascular events, FDA decided to undertake its own meta-analysis to more fully evaluate this safety signal and is working diligently to complete this very complex analysis in the next few weeks.

B. Balanced Cohort Study of Coronary Heart Disease Outcomes in Patients Receiving Anti-diabetic Agents

The Balanced Cohort Study is an observational study of 33,363 patients using a medical and pharmacy claims database (the population-based study noted above) that was conducted by GSK and submitted to FDA at the same time as the meta-analysis described above. Propensity matching was used to match risk factors for cardiovascular disease and other considerations for patients initiating therapy. About 90 percent of the patients had no history of cardiovascular disease. The composite cardiovascular endpoint for the study was hospitalizations for myocardial infarction and coronary revascularization. Patients included in this study began treatment with rosiglitazone between the years 2000 and 2004. The treatment groups were monotherapy with rosiglitazone, metformin, or sulfonylurea; oral dual therapy (two-drug) combinations, and combinations that also included insulin. Follow-up was 1.2 years. The incidence of the composite cardiovascular endpoint was 1.75 events per 100 patient-years for the rosiglitazone-containing regimens and 1.76 events per 100 patient-years for other treatments (hazard ratio 0.93; 95 percent CI 0.80-1.10). These findings are inconsistent with the results of GSK's meta-analysis in that they do not show an increased risk

of adverse cardiovascular outcomes in patients taking rosiglitazone compared to other therapies.

As submitted last August, then, GSK provided FDA with two studies (August 2006 meta-analysis study and Balanced Cohort Study) examining a large number of patients with divergent results. These results made it even more imperative that FDA examine all these data carefully and independently of the sponsor.

C. A Diabetes Outcomes Progression Trial (ADOPT)

ADOPT, a Phase IV Post-marketing Commitment study, is a randomized, double-blind study of 4,351 patients that compared rosiglitazone, metformin, or glyburide monotherapy on the improvement of and maintenance of glycemic control in patients newly diagnosed with type 2 diabetes. Patients with diagnosed cardiovascular disease were excluded. Median follow-up was four years. The myocardial ischemic event hazard ratios were: rosiglitazone vs. metformin- 0.96 (95 percent CI 0.66, 1.38); rosiglitazone vs. glyburide- 1.16 (95 percent CI 0.78, 1.73); and metformin vs. glyburide- 1.22 (95 percent CI 0.082, 1.80). The results of the ADOPT trial have been published (*New England Journal of Medicine* 355;23 pg 2427-2443 December 7, 2006). These data do not support an increased ischemic risk of rosiglitazone relative to metformin or glyburide. It is important to note that metformin is recommended by many treatment guidelines as the first line therapy for type 2 diabetes and has been shown in other long-term studies to lower cardiovascular risk. The final study report was submitted to FDA in February 2007 and is currently under review.

D. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Study

The DREAM study is a placebo-controlled, randomized, double-blind clinical trial in pre-diabetic patients designed to determine if the use of early treatment with medication could forestall the development of overt type 2 diabetes. The study was conducted in nearly 5,300 patients who were randomized to either rosiglitazone or placebo and were followed up for a mean duration of three years. The study also was intended to examine whether rosiglitazone and/or ramipril delayed onset of overt type 2 diabetes. Therefore, the trial used a factorial design, with patients randomized to any of four treatment arms: placebo; rosiglitazone; ramipril; or rosiglitazone with ramipril. This study, as reported in The Lancet, showed an effect of rosiglitazone in delaying the development of type 2 diabetes (not found with ramipril) in these pre-diabetic patients. Also, the published report noted an increased risk of cardiovascular ischemic events (30 percent) in patients treated with rosiglitazone (e.g. the rosiglitazone plus placebo and rosiglitazone plus ramipril arms). This risk was not statistically significant. It should be mentioned that the overall death rate for rosiglitazone was lower than with placebo, but that too was not statistically significant.

The DREAM study was conducted by scientists from McMaster University; GSK only recently obtained the database from McMaster for further analysis. In a recent meeting with FDA, GSK shared an analysis of the data broken out by the four individual arms of the study, data that were not reported in the published manuscript. These data showed that for rosiglitazone alone versus placebo there was no increased risk of myocardial infarction, stroke, or cardiovascular death. FDA has not yet received the DREAM study data so we

cannot independently evaluate these data at this time. FDA expects that GSK will submit the DREAM study data to FDA for more complete review in the near future.

E. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Study

The RECORD study is a large, ongoing, randomized, open-label trial evaluating cardiovascular outcomes in patients treated with rosiglitazone as add-on therapy to either metformin or sulfonylurea in comparison to add-on therapy with metformin and a sulfonylurea (patients already receiving metformin were randomized to receive add-on rosiglitazone or sulfonylurea and patients already receiving sulfonylurea were randomized to receive add-on rosiglitazone or metformin). The RECORD study is being conducted by GSK as a post-marketing commitment to the European Medicines Evaluation Agency. RECORD was designed as a non-inferiority safety study of rosiglitazone vs. combined controls with a primary endpoint of cardiovascular death and hospitalization (including congestive heart failure). Although the study is not blinded (patients and doctors know which medicine the patients are randomized to take) unlike other studies of rosiglitazone, RECORD's cardiac events are being adjudicated in a blinded fashion to treatment assignment by a Cardiovascular Endpoints Committee.

Over 300 study centers in 25 countries in Europe are involved in the conduct of this study with each center attempting to enroll 10 to 20 patients. This non-IND study (done outside the United States and without input to the protocol or study design by FDA) started in 2001 and completed enrollment in 2003, with over 4400 patients enrolled and proposed to be followed

for 5 years. The study is still ongoing with the last patient expected to reach the targeted duration of follow-up in late 2008. The study has regularly been monitored by a data monitoring committee aware of the apparent elevation in cardiovascular ischemic risk indicated by the pooled analysis, but the Committee has not called for the study to be stopped. Further, FDA has been allowed to see the results of a recent interim safety analysis and these interim data will be taken into account in FDA's considerations and actions. However, to preserve the study integrity, FDA is not explicitly commenting on these analyses.

F. Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics (BARI 2D)

BARI 2D trial is a multi-center study being conducted by the National Institutes for Health that uses a 2x2 factorial design, with 2800 patients being assigned at random to initial elective coronary artery revascularization with aggressive medical therapy or aggressive medical therapy alone, and simultaneously being assigned at random to an insulin provided or insulin sensitizing strategy of glycemic control. This latter group includes a large number of patients on rosiglitazone. FDA has not been involved actively in this study, but we do know the investigators are aware of the GSK pooled analysis and that the study has not been stopped in any interim analysis by the data monitoring committee.

G. Most Recent Meta-Analysis

As noted above, on May 21, 2007, the NEJM published another meta-analysis of rosiglitazone studies. This makes, to date, a total of three pooled or meta-analyses of rosiglitazone and the risk of ischemic cardiovascular outcomes: the one conducted by GSK, FDA's ongoing re-analysis of GSK's data, and the newly published study by

Dr. Stephen Nissen. Dr. Nissen's analysis was based on data from 42 controlled clinical trials (though this is the same number of studies as in the GSK meta-analysis many but not all, of the studies were the same). Despite their differences, conclusions of Nissen and GSK about the estimated risk of cardiac ischemia from the respective studies were similar.

Even though the GSK and Nissen analyses had similar conclusions, FDA's continuing re-analysis of GSK's data is important. The Nissen analysis was based on study-level data, while FDA's re-analysis of the GSK data is based on more detailed patient-level data. Patient-level data provide the opportunity to look more closely at how studies were conducted and better assess which diabetes patients may be at particular risk of any adverse event associated with rosiglitazone. Such data will far better inform health care providers and patients in selecting appropriate therapies. Also, it will allow for a more careful interpretation of the meta-analysis findings in light of data from the other large, individual trials (described above) whose data are emerging.

In light of the recent public attention to NEJM's publication, many have raised questions about the role of meta-analyses in FDA's regulatory decision-making. A meta-analysis is the process or technique of synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies which on their own are not large enough to examine a particular question. Meta-analyses are often informative, but have important limitations. They are complicated to conduct. Deciding the best methods of combining data, which studies to combine, and similar decisions can be

controversial. FDA has historically been cautious in the use of meta-analyses in support of regulatory decisions.

We at FDA are committed to examining all data available in answering the challenging scientific and clinical questions before us about rosiglitazone. We are continuing our own meta-analysis using rigorous statistical procedures. We will evaluate the results of that analysis along with the data from other sources, including the long-term controlled clinical trials described above and the large observational study, before reaching a conclusion about the potential for an increased risk for ischemic cardiovascular events in patients treated with rosiglitazone.

CONCLUSION

FDA's mission is to promote and protect the public health. A major component of that mission is to ensure that the American public has access to safe and effective medical products. We base decisions to approve a drug or to keep it on the market if new safety findings surface, on a careful balancing of risk and benefit, as well as consideration of the tools we have to help minimize the risks to patients from a drug's use. This multifaceted and complex decision process involves weighing both scientific and public health issues. We will continue to work diligently to assess all available data on rosiglitazone. As always, we value input from Congress, the public, and the medical community as we develop and refine these drug safety initiatives.

As I have emphasized in this statement, FDA remains committed to the thorough, timely assessment of the information needed to reach conclusions about both the benefits and risks of rosiglitazone and other drugs for diabetic patients. As a public health agency, we must evaluate the safety of medical products on the basis of how they affect the entire patient. We do not have the luxury of focusing on one organ or on one organ system.

Mr. Chairman, in this case, we wanted people not only to be aware of the potential risk, but also to understand that the evidence – not only according to FDA's best judgment but in the view of other experts as well – remains inconclusive. That means FDA is not at present justified in taking additional regulatory action or recommending that patients stop using it. We wanted patients to be aware of this developing situation and to consult with their physicians if they had concerns. It would be counterproductive indeed if patients stopped taking rosiglitazone to avoid a small and potential increased heart risk, only to incur a much greater risk from their underlying diabetes. We will, of course, revisit this position as additional data become available and are analyzed.

Thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.